ONJ

DEFINIZIONE E DIAGNOSI

Giuseppina Campisi*-Palermo
Alberto Bedogni*-Verona

**Speaker dichiarano: nessun conflitto di interesse*

TERMINOLOGIA

ONJ

MRONJ

(2014)

Phossy Jaw

Bisphosphonates and osteonecrosis: analogy to phossy jaw

A Michael Donoghue
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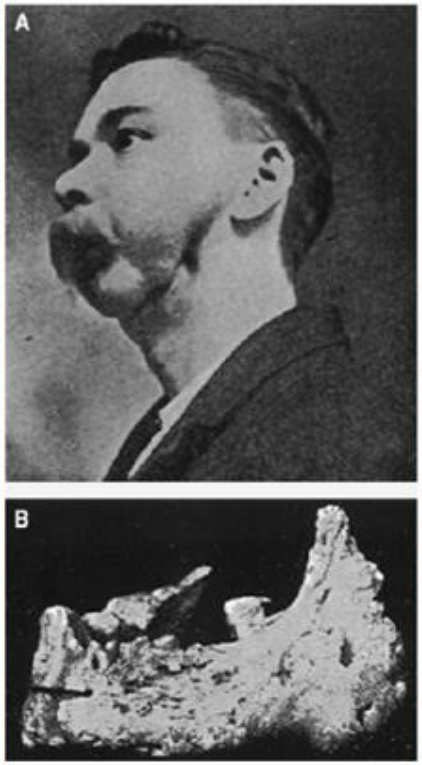
TO THE EDITOR: Osteonecrosis of the jaw, recently reported in patients treated with bisphosphonates, may be analogous to the historic occupational disease "phossy jaw".[1,2]

Phossy jaw was osteonecrosis of the jaw caused by exposure to white phosphorus during the manufacture of matches. "Lucifer" strike-anywhere matches were first produced in 1833. They were made by dipping the match ends into a mixture containing white phosphorus.[3] Workers were exposed to fumes from the white phosphorus during mixing and spreading of the dip material, and dipping, drying and boxing of the matches.[3,4]

The first case series, comprising 22 cases, was reported in Vienna in 1845.[5] About 11% of those exposed developed the disease.[5] The average period from first exposure to diagnosis was 5 years.[4,5] Occasionally, this period was as short as a few months.[5] The mandible and maxilla could be affected, the mandible in 60% of cases (Box).[3] Dental decay was considered a prerequisite, and preventive measures included dental surveillance and treatment within the factories.[4] In that pre-antibiotic era, phossy jaw was fatal in about 20% of cases, usually because of septicaemia or meningitis.[5]

Donald Hunter, British doyen of occupational medicine, commented: "It was the most distressing of all the occupational diseases because it was very painful and was accompanied by a foul fetid discharge that made its victims almost unendurable to others. It was obstinate and chronic, the treatment was agonising and the final result was a distressing disfigurement. It was this disfiguring effect plain to every observer that made phosphorus poisoning so notorious and led to determined efforts for its abolition in every civilised land."[5]

Phosphorus necrosis of the jaw



A *Deformity resulting from excision of entire lower jaw in a case of phosphorus necrosis. (Case of Dr John P. Andrews, The Occupational Diseases, W Gilman Thompson, D Appleton & Co, New York, 1914).*

B *Phosphorus necrosis of entire lower jaw excised by Mr McCarthy in 1884 (London Hospital Medical College Museum).*

Donoghue AM. Bisphosphonates and osteonecrosis: analogy to phossy jaw. Med J Aust. 2005 Aug 1;183(3):163-4.

Dr. Francesco BARTUCCI
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OGGETTO: Specialità medicinali a base di bisfosfonati
Zometa - Aredia

Egregio Dottore,

Novartis intende informarLa in merito alle recenti modifiche apportate al contenuto del *Riassunto delle caratteristiche del prodotto* di Zometa, specialità registrata con procedura centralizzata, e di Aredia, specialità registrata con procedura nazionale.

Le modifiche apportate si riferiscono alla possibile comparsa di osteonecrosi della mascella/mandibola in pazienti con cancro in trattamento con bisfosfonati, comprendenti Aredia e Zometa, come parte della terapia antitumorale.

Esse sono volte ad assicurare una gestione ottimale dei pazienti con tumori maligni allo stadio avanzato che interessano l'osso e fornire una guida per la gestione dell'osteonecrosi della mascella/mandibola (ONJ).

La maggioranza delle segnalazioni è stata successiva ad interventi odontoiatrici (per esempio estrazioni dentali o altri interventi dentali). Molte segnalazioni evidenziano anche segni di infezione locale, comprese osteomieliti.

Novartis ricorda a tutti gli operatori sanitari che, in accordo alla normativa vigente in Italia (D.L.vo 95/03), tutte le segnalazioni di sospette reazioni avverse da farmaci devono essere inviate al Responsabile di Farmacovigilanza della Struttura di appartenenza.

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Nota informativa importante su Sunitinib (Sutent) del 30/11/2010

Sicurezza

30/11/2010

Disponibili on line nuove e importanti informazioni di sicurezza relative al Sunitinib (Sutent):

In sintesi:

- Casi di osteonecrosi della mascella sono stati segnalati in pazienti con tumore trattati con Sutent; nella maggior parte dei casi segnalati i pazienti avevano ricevuto precedentemente o contemporaneamente un trattamento con bifosfonati per via endovenosa.
- Il trattamento con Sutent può essere un ***fattore di rischio*** aggiuntivo per lo sviluppo dell'osteonecrosi della mascella.
- Il rischio potenziale deve essere considerato in particolar modo quando Sutent e i bifosfonati sono somministrati contemporaneamente o in sequenza Prima del trattamento con Sutent si devono considerare una visita odontoiatrica ed appropriate cure odontoiatriche preventive. Nei pazienti che hanno ricevuto precedentemente o che sono in trattamento con bifosfonati e.v. dovrebbero essere evitate, se possibile, procedure dentistiche invasive.

Nella Nota Informativa Importante allegata sono riportate notizie più esaustive su questa problematica e raccomandazioni per gli operatori sanitari.

Allegati

Nota informativa importante sul Sunitinib (Sutent)

Principi attivi correlati

- Sunitinib

www.agenziafarmaco.gov.it/it/content/nota-informativa-importante-su-avastin-bevacizumab-del-30112010

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Attività

- Registrazione
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Nota Informativa Importante su Avastin (bevacizumab) del 30/11/2010

Sicurezza

30/11/2010

Nuove e importanti informazioni di sicurezza su Avastin (bevacizumab).

In sintesi:

- Casi di osteonecrosi della mascella sono stati segnalati in pazienti oncologici trattati con Avastin; nella maggior parte dei casi segnalati i pazienti avevano ricevuto precedentemente o contemporaneamente un trattamento con bifosfonati per via endovenosa.
- Il trattamento con Avastin può essere un ***fattore di rischio*** aggiuntivo per lo sviluppo dell'osteonecrosi della mascella.
- Il rischio potenziale deve essere considerato in particolar modo quando Avastin e i bifosfonati sono somministrati contemporaneamente o in sequenza.
- Prima del trattamento con Avastin devono essere considerate il ricorso a una valutazione odontoiatrica e un'appropriata prevenzione odontoiatrica. Se possibile, le procedure odontoiatriche invasive devono essere evitate nei pazienti che hanno ricevuto precedentemente o che sono in trattamento con bifosfonati per via e.v.

Nella Nota Informativa Importante allegata sono riportate notizie più esaustive su questa problematica in oggetto e le raccomandazioni per gli operatori sanitari.

Allegati

Nota informativa importante su Avastin (bevacizumab)

Principi attivi correlati

- Bevacizumab

P.R.O.Ma.B.

Prevenzione e Ricerca sull'Osteonecrosi
dei Mascellari da Bisfosfonati

Documento informativo ad ampia divulgazione per l'approfondimento dell'osteonecrosi dei mascellari determinata dall'utilizzo di bisfosfonati

2012

Proposta e redatta da	**U.O.S. DI MEDICINA ORALE (35.01.04)** **[U.O.C. DI ODONTOSTOMATOLOGIA (35.01.0) del Dipartimento Scienze Specialistiche Medico-Chirurgiche e Riabilitative]** *Prof. G. Campisi – Professore Straordinario - Dirigente Medico I Livello* *Dott. O. Di Fede - Ricercatore- Odontoiatra frequentatore* *per il percorso preferenziale aziendale* AOUP "P. Giaccone" Palermo *PROMaB* **Prevenzione e Ricerca sull'Osteonecrosi dei Mascellari da Bisfosfonati**
Validata da	Direzione Sanitaria AOUP "P. Giaccone" Palermo

Infine, per il principio di cautela e viste le recenti note AIFA relative alla somministrazione di sunitinib (http://www.agenziafarmaco.gov.it/it/content/nota-informativa-importante-su-sunitinib-sutent-30112010) e di bevacizumab (http://www.agenziafarmaco.gov.it/it/content/nota-informativa-importante-su-avastin-bevacizumab-30112010), si consiglia di **applicare queste raccomandazioni anche in pazienti che necessitano l'assunzione di farmaci a cosiddetto target biologico** (e.g. sunitinib, bevacizumab) per la prevenzione della osteonecrosi delle ossa mascellari.

Alberto Bedogni Giuseppina Campisi Vittorio Fusco Alessandro Agrillo

Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione

Società Italiana di Chirurgia Maxillo-Facciale (SICMF)
Società Italiana di Patologia e Medicina Orale (SIPMO)

2013

2013

DENTAL CADMOS | 2013;81(9):566-589 | 567

Patologia e Medicina orale

Osteonecrosi dei mascellari associata a bisfosfonati, denosumab e farmaci anti-angiogenetici nei pazienti oncologici e osteoporotici: diagnosi e terapia

Osteonecrosis of the jaw related to bisphosphonates, denosumab and anti-angiogenics in cancer and osteoporotic patients: diagnosis and management

G. Campisi[a*], A. Bedogni[b], O. Di Fede[a], P. Vescovi[c], V. Fusco[d], L. Lo Muzio[e]

Key words: *Jaw osteonecrosis | Bisphosphonates | Anti-angiogenics | Denosumab | Oral pathology*

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Future Oncol. 2014 Feb;10(2):257-75. doi: 10.2217/fon.13.211.

Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents.

Campisi G[1], Fedele S, Fusco V, Pizzo G, Di Fede O, Bedogni A.

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Abstract

Osteonecrosis of the jaws (ONJ) is an adverse side event of bisphosphonates and denosumab, antiresorptive agents that effectively reduce the incidence of skeletal-related events in patients with metastatic bone cancer and multiple myeloma. Available data suggest that 0-27.5% of individuals exposed to antiresorptive agents can develop ONJ. There is increasing evidence that avoidance of surgical trauma and infection to the jawbones can minimize the risk of ONJ, but there are still a significant number of individuals who develop ONJ in the absence of these risk factors. Bone necrosis is almost irreversible and there is no definitive cure for ONJ with the exclusion, in certain cases, of surgical resection. However, most ONJ individuals are affected by advanced incurable cancer and are often managed with minimally invasive nonsurgical interventions in order to control jawbone infections and painful symptoms. This article summarizes current knowledge of ONJ epidemiology, manifestations, risk-reduction and therapeutic strategies. Further research is needed in order to determine individual predisposition to ONJ and clarify the effectiveness of available treatments.

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REVIEW

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Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents

feb 2014

Giuseppina Campisi*[1], Stefano Fedele[2], Vittorio Fusco[3], Giuseppe Pizzo[1], Olga Di Fede[1] & Alberto Bedogni[4]

ABSTRACT Osteonecrosis of the jaws (ONJ) is an adverse side event of bisphosphonates and denosumab, antiresorptive agents that effectively reduce the incidence of skeletal-related events in patients with metastatic bone cancer and multiple myeloma. Available data suggest that 0–27.5% of individuals exposed to antiresorptive agents can develop ONJ. There is increasing evidence that avoidance of surgical trauma and infection to the jawbones can minimize the risk of ONJ, but there are still a significant number of individuals who develop ONJ in the absence of these risk factors. Bone necrosis is almost irreversible and there is no definitive cure for ONJ with the exclusion, in certain cases, of surgical resection. However, most ONJ individuals are affected by advanced incurable cancer and are often managed with minimally invasive nonsurgical interventions in order to control jawbone infections and painful symptoms. This article summarizes current knowledge of ONJ epidemiology, manifestations, risk-reduction and therapeutic strategies. Further research is needed in order to determine individual predisposition to ONJ and clarify the effectiveness of available treatments.

Ministero della Salute

Dipartimento della sanità pubblica e dell'innovazione

Raccomandazioni per la promozione della salute orale, la prevenzione delle patologie orali e la terapia odontostomatologica nei pazienti adulti con malattia neoplastica.

aprile 2014

9. APPENDICE

PREVENZIONE ODONTOIATRICA E SICUREZZA DEI TRATTAMENTI ODONTOIATRICI NEI PAZIENTI CON MALATTIA NEOPLASTICA TRATTATI CON BISFOSFONATI, DENOSUMAB E/O ANTI-ANGIOGENETICI.

OSTEONECROSI DEI MASCELLARI ASSOCIATA A BISFOSFONATI - BRONJ

L'osteonecrosi dei mascellari associata a bisfosfonati (BRONJ) è stata definita come "una reazione avversa farmaco-correlata, caratterizzata dalla progressiva distruzione e necrosi dell'osso mandibolare e/o mascellare di soggetti esposti al trattamento con aminobisfosfonati, in assenza di un precedente trattamento radiante" (Bedogni, Fusco et al. 2012; Bedogni, Campisi et al. 2013).

OSTEONECROSI DEI MASCELLARI ASSOCIATA A DENOSUMAB O FARMACI ANTIANGIOGENETICI

Recentemente la ONJ è stata osservata in pazienti oncologici anche in corso di terapie con altri farmaci anti-resorptive (i.e. denosumab) (Pichardo, Kuypers et al. 2012; Rachner, Platzbecker et al. 2013) o con anti-angiogenetici (Troeltzsch, Woodlock et al. 2012), quest'ultimi sia in combinazione con BP che senza l'uso concomitante di BP.

Appendix I: Antiresorptive Preparations Commonly Used in the U.S.

Position Paper

May 2014

	Primary Indication	Nitrogen Containing	Dose	Route
Alendronate (Fosamax®)	Osteoporosis	Yes	10 mg/day 70 mg/week	Oral
Risedronate (Actonel®)	Osteoporosis	Yes	5 mg/day 35 mg/week	Oral
Ibandronate (Boniva®)	Osteoporosis	Yes	2.5 mg/day 150 mg/month 3 mg every 3 months	Oral IV
Pamidronate (Aredia®)	Bone Metastases	Yes	90 mg/3 weeks	IV
Zolendronate (Zometa®) (Reclast®)	Bone Metastases Osteoporosis	Yes	4 mg/3 weeks 5 mg/year	IV IV
Denosumab (Xgeva®) (Prolia®)	Bone metastases Osteoporosis	No Humanized monoclonal antibody	120 mg/4 weeks 60 mg/6 months	SQ SQ

http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper

Position Paper

Appendix II: Medications Used in the Treatment of Various Cancer: Antiangiogenic or Targets of the Vascular Endothelial Growth Factor Pathway that have been Associated with Jaw Necrosis*.

Drug	Mechanism of action	Primary indication
Sunitinib (Sutent®)	Tyrosine kinase inhibitor	GIST, RCC, pNET
Sorafenib (Nexavar®)	Tyrosine kinase inhibitor	HCC, RCC
Bevacizumab (Avastin®)	Humanized monoclonal antibody	mCRC, NSCLC, Glio, mRCC
Sirolimus (Rapamune®)	Mammalian target of rapamycin pathway	Organ rejection in renal transplant

Abbreviations: GIST gastrointestinal stromal tumor; RCC renal cell carcinoma; pNET pancreatic neuroendocrine tumor, HCC hepatocellular carcinoma; mCRC metastatic colorectal carcinoma; NSCLC non-squamous non-small cell lung carcinoma; Glio Glioblastoma; mRCC metastatic renal cell carcinoma

* While the FDA has issued an ONJ advisory only for bevacizumab and sunitinib,[99,100] the committee remains concerned about a similar potential risk associated with several other medications within the same drug class which have a similar mechanism of action. Therefore further controlled, prospective studies will be required to more fully characterize the risk of jaw necrosis associated with these agents.

May 2014

http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper

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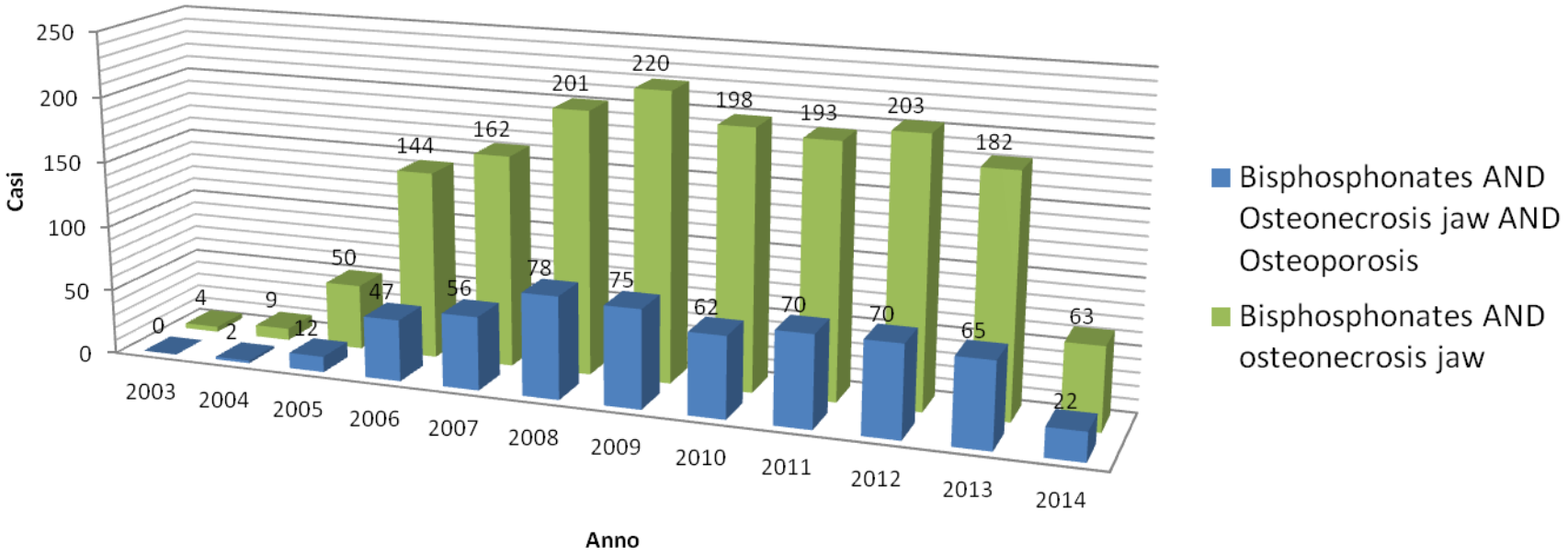

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
BP + ONJ + Osteoporosis	0	2	12	47	56	78	75	62	70	70	65	22
BP + ONJ	4	9	50	144	162	201	220	198	193	203	182	63

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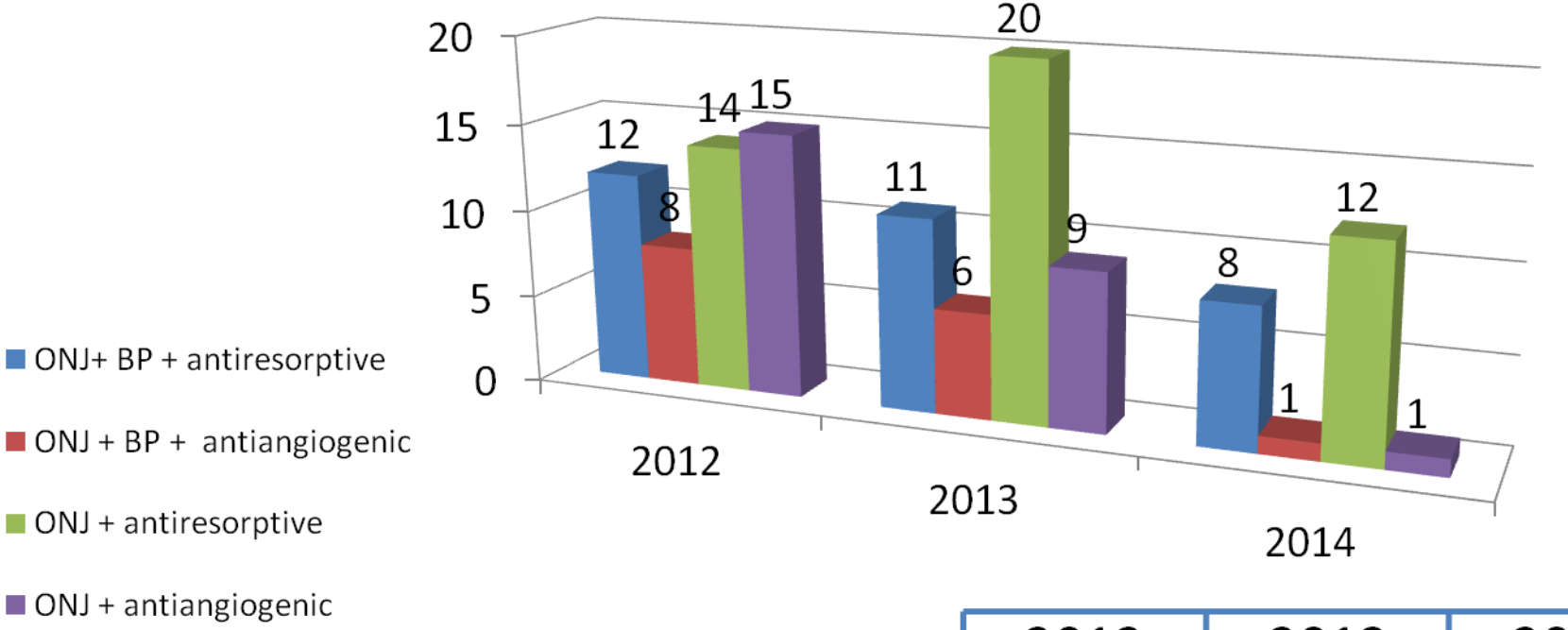

	2012	2013	2014
ONJ+ BP + antiresorptive	12	11	8
ONJ + BP + antiangiogenic	8	6	1
ONJ + antiresorptive	14	20	12
ONJ + antiangiogenic	15	9	1

Bone 58 (2014) 103–107

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Clinical study evaluating the effect of bevacizumab on the severity of zoledronic acid-related osteonecrosis of the jaw in cancer patients☆

Géraldine Lescaille[a,b,*,1], Amélie E. Coudert[c,1], Vanessa Baaroun[a,c], Agnès Ostertag[d], Emmanuel Charpentier[a], Marie-José Javelot[a], Rafael Tolédo[a], Patrick Goudot[e], Jean Azérad[a], Ariane Berdal[c], Jean-Philippe Spano[f], Blandine Rubin[e], Vianney Descroix[a,c]

ABSTRACT

This study aimed to evaluate the effect of bevacizumab (BVZ) on the severity of osteonecrosis of the jaw (ONJ) in a cohort of cancer patients treated with intravenous zoledronic acid (ZA). We reviewed 42 oncologic patients with ONJ between 2007 and 2010. Only patients with solids tumors and who had received ZA were included. Data analyses included age, sex, underlying disease, ZA and BVZ dosages, dental history and ONJ characteristics. Of the 42 ONJ patients treated with ZA, 10 also received BVZ. In the 10 ZA/BVZ patients, the mean duration of ZA treatment at the time of ONJ diagnosis was 12.4 months (±6.8), compared to 22.9 months (±4.8) in the 32 patients who received ZA only ($p<0.05$). Cox's model analysis of the delay to ONJ diagnosis confirmed the impact of BVZ on ONJ diagnosis. In the ZA/BVZ-treated group, 7 (70%) patients developed spontaneous osteonecrosis. Multiple logistic regression analysis showed that ZA/BVZ is associated with increased risk of developing spontaneous ONJ (OR 6.07; 95% CI, [1.3–28.2], $p<0.05$). And finally, the number of ONJ lesions was increased in the ZA/BVZ-treated group compared to the ZA group ($p<0.01$). Other clinical conditions as type of tumor (prostate, breast...), cancer severity or other chemotherapy drugs also could be involved in ONJ evolution. However, this study demonstrates for the first time the potential negative influence of BVZ on the incidence and severity of ONJ in patients receiving ZA. Within the study limits, our results suggest that combination ZA/BVZ treatment may possibly predispose to the development of spontaneous and earlier ONJ.

2014

Testosterone, anastrozole, factor V Leiden heterozygosity and osteonecrosis of the jaws

Ramesh S. Pandit and Charles J. Glueck

Our specific aim is to describe the development of thrombotic osteonecrosis of the jaws after testosterone–anastrozole therapy in a 55-year-old white man subsequently found to have previously undiagnosed factor V Leiden heterozygosity. Before the diagnosis of V Leiden heterozygosity, he was given testosterone gel, 50 mg/day, and on testosterone, serum testosterone (963 ng/dl) and estradiol were high (50 pg/ml). Anastrozole was started, and testosterone was continued. Six months later, osteonecrosis of the jaws was diagnosed. Exogenous testosterone is aromatized to estradiol and estradiol-induced thrombophilia, when superimposed on underlying familial thrombophilia, as in this case, may lead to thrombosis and osteonecrosis. We recommend that before giving testosterone, at a minimum, screening for the factor V Leiden and G20210A mutations, and factor VIII and XI activity be carried out, to avoid unanticipated thrombosis.

Blood Coagul Fibrinolysis 25:286–288 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Blood Coagulation and Fibrinolysis 2014, 25:286–288

Keywords: anastrozole, anticardiolipin antibody, deep venous thrombosis-pulmonary embolus, factor V Leiden heterozygosity, hypofibrinolysis, methylenetetrahydrofolate/reductase mutation, osteonecrosis of jaws, primary thrombophilia, testosterone

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Correspondence to Charles J. Glueck, MD, The Cholesterol and Metabolism Center, 2135 Dana Avenue, Suite 430, Cincinnati, OH 45207, USA
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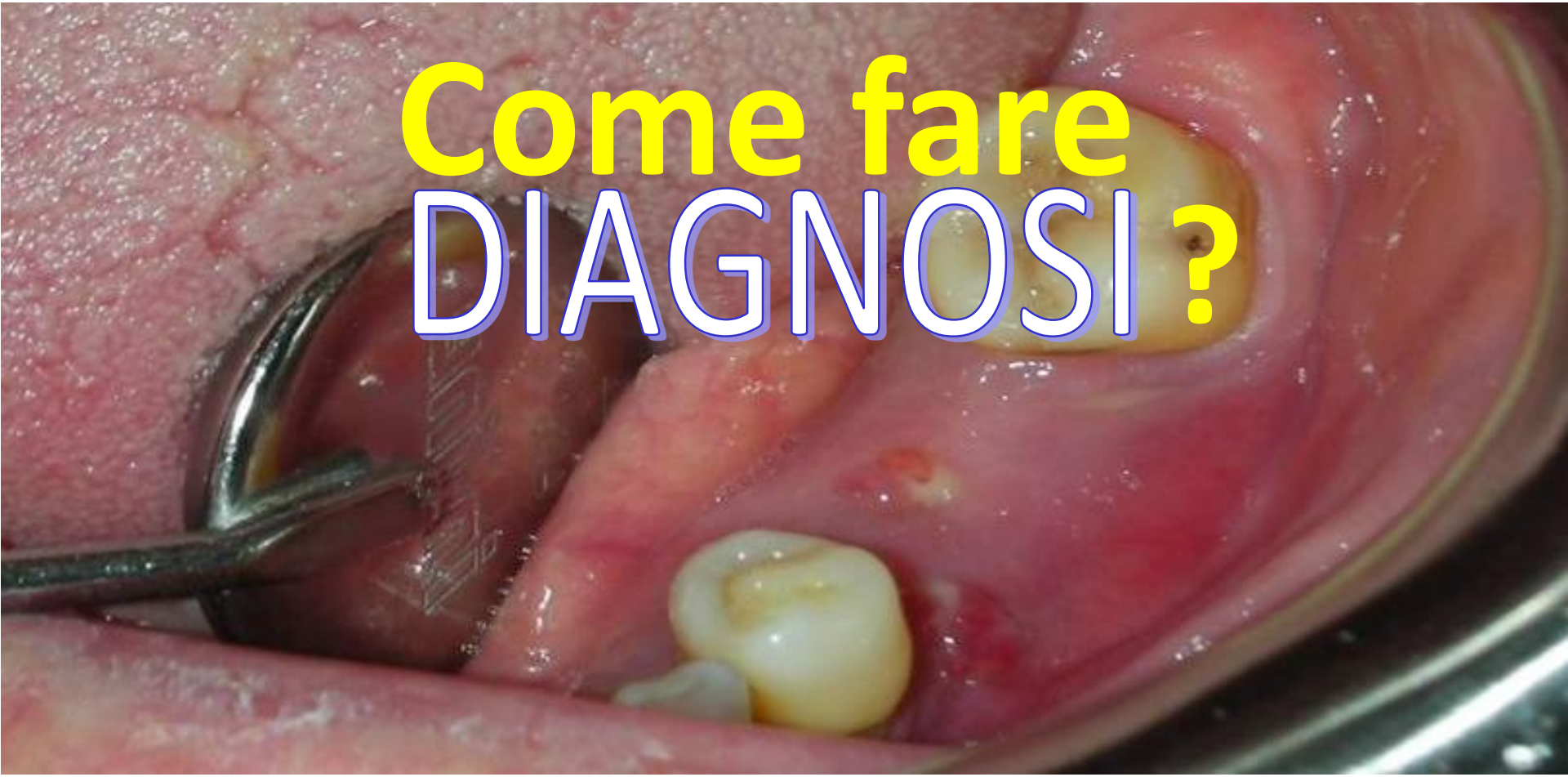
Accepted 20 November 2013



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Definizione di BRONJ (AAOMS 2007-09)

"***Osso necrotico*** *esposto in cavo orale per più di* ***8 settimane*** *dalla sua identificazione da parte di uno specialista, in un paziente in* ***terapia con bisfosfonati*** *(pregressa o in atto),* ***mai*** *sottoposto a* ***radioterapia dei mascellari*** *(testa-collo)*"

- **ASBMR 2008**
- **CAOMS 2008**
- **French Expert Panel Analysis 2009**
- **EMEA 2009**
- **Japanese Allied Committee 2010**

Un gruppo di esperti del BRONJ panel of the Italian Society for Maxillofacial Surgery (SICMF) and the Italian Society of Oral Pathology and Medicine (SIPMO) on Bisphosphonate-Related Osteonecrosis of the Jaws hanno di recente pubblicato su

ORAL DISEASES

Learning from experience. Proposal of a refined definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ)

A Bedogni[1,†,‡], V Fusco[2,†], A Agrillo[3,†], G Campisi[4,†]

puoi accedere al full text dal link

Article first published online: 22 FEB 2012

DOI: 10.1111/j.1601-0825.2012.01903.x

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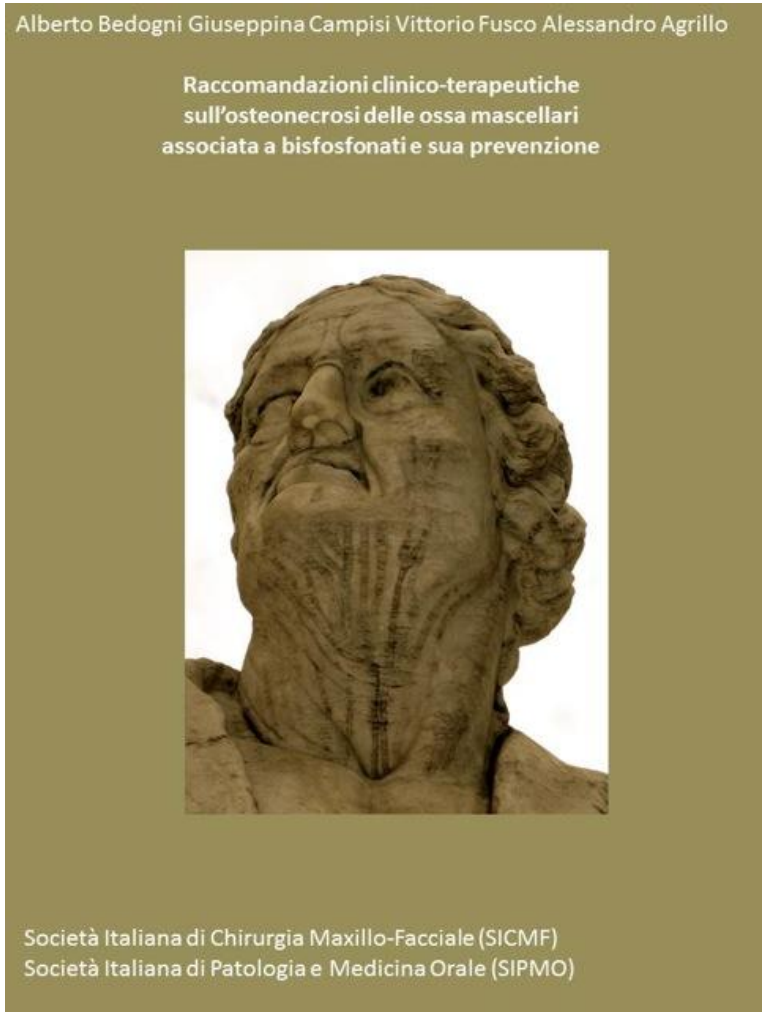
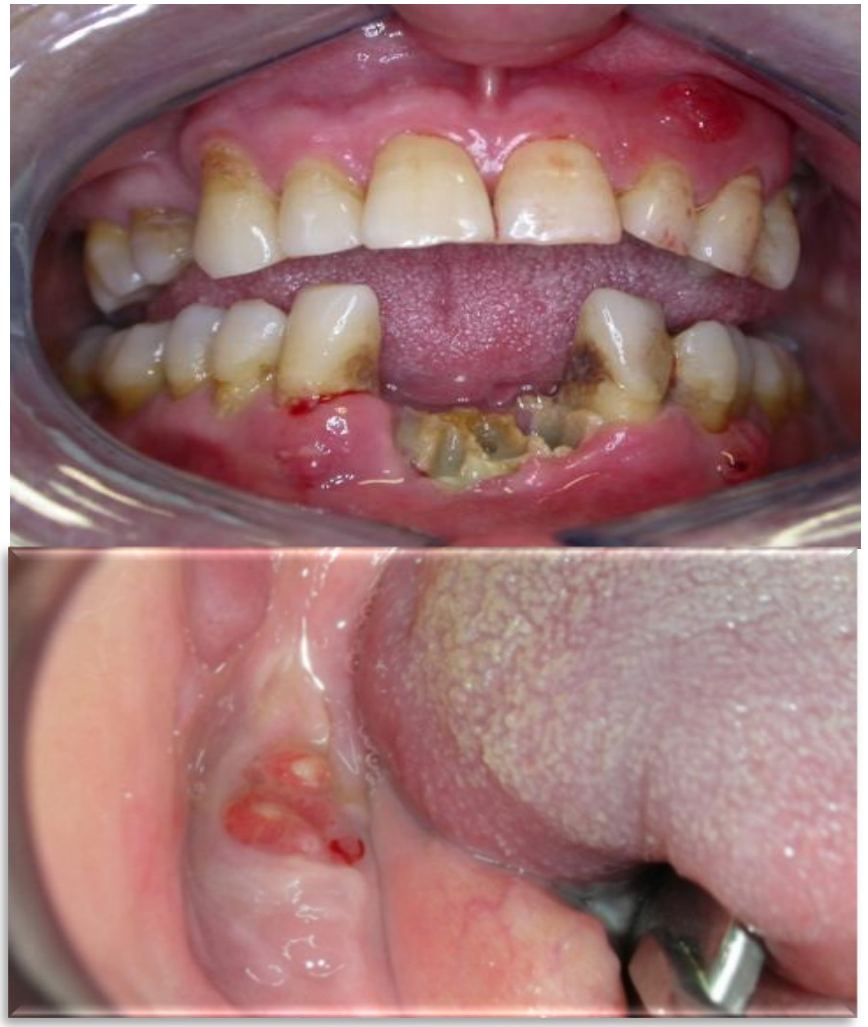
Definizione delle società scientifiche

SICMF-SIPMO (2012)

BRONJ

*“ ….è una **reazione avversa farmaco-correlata**, che colpisce l'osso mandibolare e/o mascellare di **soggetti esposti** al trattamento con amino-bisfosfonati **(NBP)**, in assenza di un pregresso trattamento radiante”*





Come si evince dalla definizione di BRONJ proposta dagli autori, l'assunzione pregressa o in atto di NBP è una condizione necessaria per poter identificare soggetti a rischio e potenzialmente affetti dalla malattia (Appendice I). Tale condizione, pur tuttavia, non è mai sufficiente a porre da sola una diagnosi conclusiva di BRONJ.

CRITERI DI INCLUSIONE

Terapia in atto o pregressa con

- **NBP (orali/endovenosi)**
- **altri antiriassorbitivi e antiangiogenetici**

CRITERI DI ESCLUSIONE

- **Pregressa o coesistente radioterapia del distretto testa-collo**

CRITERI DI DUBBIO

- **Compresenza di neoplasia ossea primitiva dei mascellari**
- **Compresenza di metastasi ossee a carico dei mascellari**

Title: Up to a quarter of patients with jaw osteonecrosis associated with antiresorptive agents can escape traditional case definition and remain undiagnosed

Article Type: Full Length Article

Section/Category: Pathology

Corresponding Author: Dr. Stefano Fedele, DDS, PhD

Corresponding Author's Institution: University College London/University College London Hospitals Trust

First Author: Stefano Fedele, DDS, PhD

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Abstract: Purpose: Recent data suggest that traditional definition of jaw osteonecrosis (ONJ) associated with bisphosphonates may be incomplete and exclude those individuals presenting with the non-exposed variant of ONJ. We tested the hypothesis that a proportion of individuals with ONJ escape traditional case definition and remain undiagnosed.
Methods: Secondary analysis of data belonging to MISSION, a cross-sectional study of a large population of individuals with bisphosphonate-associated ONJ recruited in 13 European centres. Inclusion criteria were both exposed and non-exposed ONJ. The main outcome was to quantify the proportion of ONJ patients who would not be adjudicated as having jaw osteonecrosis according to traditional ONJ definition (outcome variable) because of the absence of necrotic bone exposure (predictor variable). We also evaluated the similarity of patients with exposed and non-exposed ONJ (predictor) for selected clinical characteristics (outcome variables). Data analysis included descriptive statistics, median regression and Fisher's exact test.
Results: The original study sample was composed of 886 consecutive individuals with bisphosphonate-associated ONJ, of which 799 subjects met the inclusion criteria and comprise the sample for analyses. Among them, 607 (76.0%) were adjudicated as having ONJ based on traditional definition. The remaining 192 (24.0%) could not be adjudicated, as they had a number of abnormal features to the jawbones but no evidence of necrotic bone exposure. The two groups were similar for most phenotypic variables tested.
Conclusion: This is the first study that shows that case adjudication based on the traditional definition may translate into one fourth of osteonecrosis cases remaining undiagnosed. The non-adjudicated subjects were individuals with non-exposed variant of ONJ. These findings point out the importance of complementing the traditional case definition with that of non-exposed osteonecrosis.

Table 2 - Comparison of categorical measurements of individuals with exposed vs non-exposed osteonecrosis of the jaw

	Exposed ONJ (*N* = 607)		Non-exposed ONJ (*N* = 192)		Fisher's Exact test
	n	%	*n*	%	*p*-value
Male gender	206	34	51	27	0.06
Zoledronate	484	80	137	71	0.02
Pamidronate	70	12	29	15	0.21
Alendronate	81	13	44	23	0.002
Neridronate	2	0.3	0	0	NA
Risedronate	10	1.6	5	2.6	0.37
Ibandronate	21	3.5	9	4.7	0.51
Other BP	250	41	93	48	0.08
Steroids	175	29	49	26	0.41
Mandible	383	63	135	70	0.07
Maxilla	224	37	57	30	0.07
Pain	489	81	134	70	0.003
Cancer (all)	345	57	99	52	0.21
Breast cancer	192	32	64	33	0.66
Myeloma	166	27	44	23	0.26
Osteoporosis	91	15	48	25	0.002
Tooth extraction	348	57	86	45	0.003
Dental infection	82	14	43	22	0.004

Abbreviations: ONJ= osteonecrosis of the jaws; BP= bisphosphonates.
NA= not available

ORAL DISEASES

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INVITED MEDICAL REVIEW

Non-exposed bisphosphonate-related osteonecrosis of the jaw: a critical assessment of current definition, staging, and treatment guidelines

S Patel[1], S Choyee[2], J Uyanne[3], AL Nguyen[4], P Lee[4], PP Sedghizadeh[1], SKS Kumar[1], J Lytle[3], S Shi[4], AD Le[2,3,4]

Non-exposed bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a newly reported complication arising from bisphosphonate therapy that presents with atypical symptoms and no apparent mucosal fenestration or exposure of necrotic bone. The clinical observation of the presence of necrotic bone underneath normal epithelial coverage was not conclusive for the diagnosis of BRONJ based on current guidelines established by the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the American Society for Bone and Mineral Research (ASBMR), which specify the presence of clinically exposed necrotic bone for more than 8 weeks. Hence, the purpose of this review is to critically assess the current guidelines for diagnosis and management of BRONJ and propose a modified staging system and treatment guidelines to properly address the non-exposed variant of BRONJ lesions.

Oral Diseases (2012) **18**, 625–632

Vol. 117 No. 2 February 2014

Comparison of nonexposed and exposed bisphosphonate-induced osteonecrosis of the jaws: a retrospective analysis from the Copenhagen cohort and a proposal for an updated classification system

Morten Schiodt, DDS, Dr.odont,[a] Jesper Reibel, DDS, Dr.odont, PhD,[b] Peter Oturai, MD,[c] and Thomas Kofod, DDS, PhD[d]

Rigshospitalet and University of Copenhagen, Copenhagen, Denmark

Objective. Nonexposed osteonecrosis of the jaws (NE-ONJ) does not fit into the current definition of osteonecrosis, which requires exposed bone. A modification of the classification of bisphosphonate-induced osteonecrosis of the jaws (ONJ) is proposed. This study aimed to test proposed criteria for NE-ONJ and compare NE-ONJ with exposed ONJ (E-ONJ) in a retrospective analysis.

Study Design. In 102 patients with E-ONJ diagnosed according to Ruggiero et al. (2006, 2009), criteria for NE-ONJ were developed. Subgroups of NE-ONJ and E-ONJ were tested against each other using nonparametric and parametric statistics.

Results. Among 102 patients with ONJ, 14 had NE-ONJ and 88 had E-ONJ. NE-ONJ and E-ONJ were similar in all important data ($P > .05$) except bone exposure.

Conclusions. NE-ONJ belongs to the same disease condition as E-ONJ. NE-ONJ may be otherwise classified as ONJ stage 1, 2, or 3 and is different from ONJ stage 0. We propose to include the criteria for NE-ONJ into the classification. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:204-213)

BRONJ: Bisphoshonates Related Osteonecrosis of the Jaws

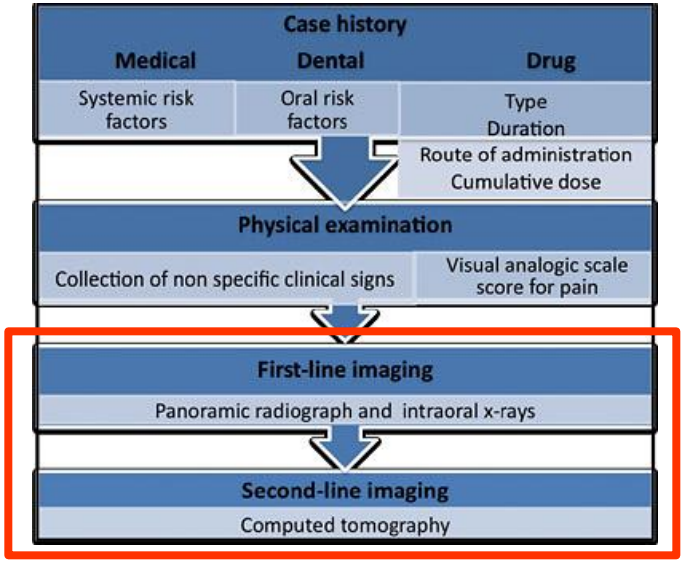
SPMO SICMF Società Italiana Chirurgia Maxillo-Facciale www.sicmf.org

Proposal of definition and staging system 2012

"BRONJ is an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible or maxilla of patients exposed to the treatment with nitrogen-containing bisphosphonates, in the absence of a previous radiation treatment" [1].

Major clinic sign

Necrotic bone exposure in oral cavity



Minor clinical signs and symptoms

- Abscess
- Displaced mandibular stumps
- Extra-oral fistula
- Gross mandible deformity
- Hypoesthesia/paraesthesia of the lips[a]
- Mucosal/gengival fistula
- Nasal leakage of fluids
- Nonhealing postextraction socket

Table 2 Non-specific computed tomography (CT) findings associated with bisphosphonate-related osteonecrosis of the jaws (BRONJ)

Early signs	*Late signs*
Cortical disruption	Diffuse osteosclerosis[b]
Focal bone marrow sclerosis[a]	Oro-antral fistula
Markedly thickened and sclerotic lamina dura	Osteolysis extending to the sinus floor
Persisting alveolar socket	Osteosclerosis of adjacent bones (zygoma, hard palate)
Trabecular thickening[a]	Pathologic fracture
	Periosteal reaction
	Prominence of the inferior alveolar nerve canal
Sequestra formation	Sinusitis

[1] Bedogni, A et al. (2012). Learning from experience. Proposal of a refined definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ). *Oral Dis* 18(6): 621-623

SICMF SIPMO Staging System – SS-SS

(Cinical-radiological stadiation of BRONJ)

Stage 1	**Focal BRONJ** **Clinical signs and symptoms:** bone exposure; sudden dental mobility; nonhealing postextraction socket; mucosal fistula; swelling; abscess formation; trismus; gross mandibular deformity and⁄or hypoesthesia⁄paraesthesia of the lips **CT findings:** increased bone density limited to the alveolar bone region (trabecular thickening and⁄or focal osteosclerosis), with or without the following signs: markedly thickened and sclerotic lamina dura; persisting alveolar socket; and⁄orcortical disruption **1a.** Asymptomatic **1b.** Symptomatic (pain and purulent discharge**)**
Stage 2	**Diffuse BRONJ** **Clinical signs and symptoms:** same as Stage 1 **CT findings**: increased bone density extended to the basal bone (diffuse osteosclerosis), with or without the following signs: prominence of the inferior alveolar nerve canal; periosteal reaction; sinusitis; sequestra formation; and⁄or oro-antral fistula **2a.** Asymptomatic **2b.** Symptomatic (pain and purulent discharge)
Stage 3	**Complicated BRONJ** Same as Stage 2, with one or more of the following: **Clinical signs and symptoms:** extra-oral fistula; displaced mandibular stumps; nasal leakage of fluids **CT findings**: osteosclerosis of adjacent bones (zygoma, hard palate); pathologic mandibular fracture; and⁄or osteolysis extending to the sinus floor

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British Journal of Oral and Maxillofacial Surgery xxx (2014) xxx–xxx
in press

ELSEVIER

Staging of osteonecrosis of the jaw requires computed tomography for accurate definition of the extent of bony disease

BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Bedogni Alberto[a,*], Fedele Stefano[b], Bedogni Giorgio[c], Scoletta Matteo[d], Favia Gianfranco[e], Colella Giuseppe[f], Agrillo Alessandro[g], Bettini Giordana[h], Di Fede Olga[i], Oteri Giacomo[j], Fusco Vittorio[k], Gabriele Mario[l], Ottolenghi Livia[m], Valsecchi Stefano[n], Porter Stephen[o], Petruzzi Massimo[p], Arduino Paolo[q], D'Amato Salvatore[r], Ungari Claudio[s], Fung Polly Pok-Lam[t], Saia Giorgia[u], Campisi Giuseppina[v]

Abstract

Management of osteonecrosis of the jaw associated with antiresorptive agents is challenging, and outcomes are unpredictable. The severity of disease is the main guide to management, and can help to predict prognosis. Most available staging systems for osteonecrosis, including the widely-used American Association of Oral and Maxillofacial Surgeons (AAOMS) system, classify severity on the basis of clinical and radiographic findings. However, clinical inspection and radiography are limited in their ability to identify the extent of necrotic bone disease compared with computed tomography (CT). We have organised a large multicentre retrospective study (known as MISSION) to investigate the agreement between the AAOMS staging system and the extent of osteonecrosis of the jaw (focal compared with diffuse involvement of bone) as detected on CT. We studied 799 patients with detailed clinical phenotyping who had had CT images taken. Features of diffuse bone disease were identified on CT within all AAOMS stages (20%, 8%, 48%, and 24% of patients in stages 0, 1, 2, and 3, respectively). Of the patients classified as stage 0, 110/192 (57%) had diffuse disease on CT, and about 1in 3 with CT evidence of diffuse bone disease was misclassified by the AAOMS system as having stages 0 and 1 osteonecrosis. In addition, more than a third of patients with AAOMS stage 2 (142/405, 35%) had focal bone disease on CT. We conclude that the AAOMS staging system does not correctly identify the extent of bony disease in patients with osteonecrosis of the jaw.
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Table 3
Number of patients with local or diffuse bone disease on computed tomography for each American Association of Oral and Maxillofacial Surgeons' stage. Data are number (%).

Stages	Focal	Diffuse	Total
0	82 (32)	110 (20)	192 (24)
1	30 (12)	42 (8)	72 (9)
2	142 (56)	263 (48)	405 (51)
3	0	130 (24)	130 (16)
Total	254 (100)	545 (100)	799 (100)


20
30
40
50

Position Paper

MRONJ Case Definition

In order to distinguish MRONJ from other delayed healing conditions and address evolving clinical observations and concerns about under-reporting of disease, the working definition of MRONJ has been modified from the 2009 *AAOMS Position Paper*:[1]

2014

Patients may be considered to have MRONJ if all of the following characteristics are present:

1. Current or previous treatment with antiresorptive or antiangiogenic agents;
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks; and

3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper

BRONJ: Bisphoshonates Related Osteonecrosis of the Jaws

saving faces | changing lives®

American Association of Oral and Maxillofacial Surgeons

POSITION PAPER 2009

"*Patients may be considered to have BRONJ if all of the following three characteristics are present:*

1. Current or previous treatment with a bisphosphonate;
2. ***Exposed bone in the maxillofacial region that has persisted for more than 8 weeks***
3. No history of radiation therapy to the jaws." [1].

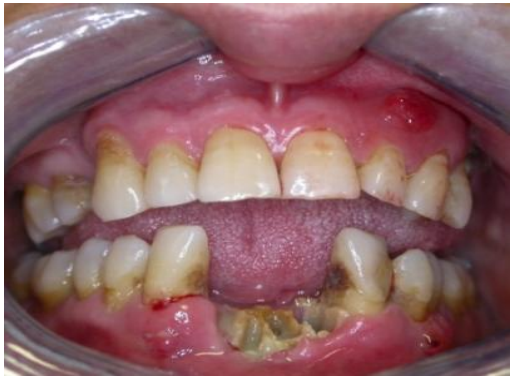
[1] Ruggiero SL et al. AAOMS position paper on bisphosphonate-related osteonecrosis of the jaws--2009 update. J Oral Maxillofac Surg. 2009 May;67(5):2-12.

POSITION PAPER 2014

"…associated with other **antiresorptive** (denosumab) and **antiangiogenic** therapies" [2].

[2] Ruggiero et al. Medication osteonecrosis of the jaws- update 2014. (http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf ?pdf=MRONJ-Position-Paper)

Medication
Related
Osteo
Necrosis of the
Jaw



AAOMS Staging System – (AAOMS-SS)

(Cinical stadiation of BRONJ/MRONJ)

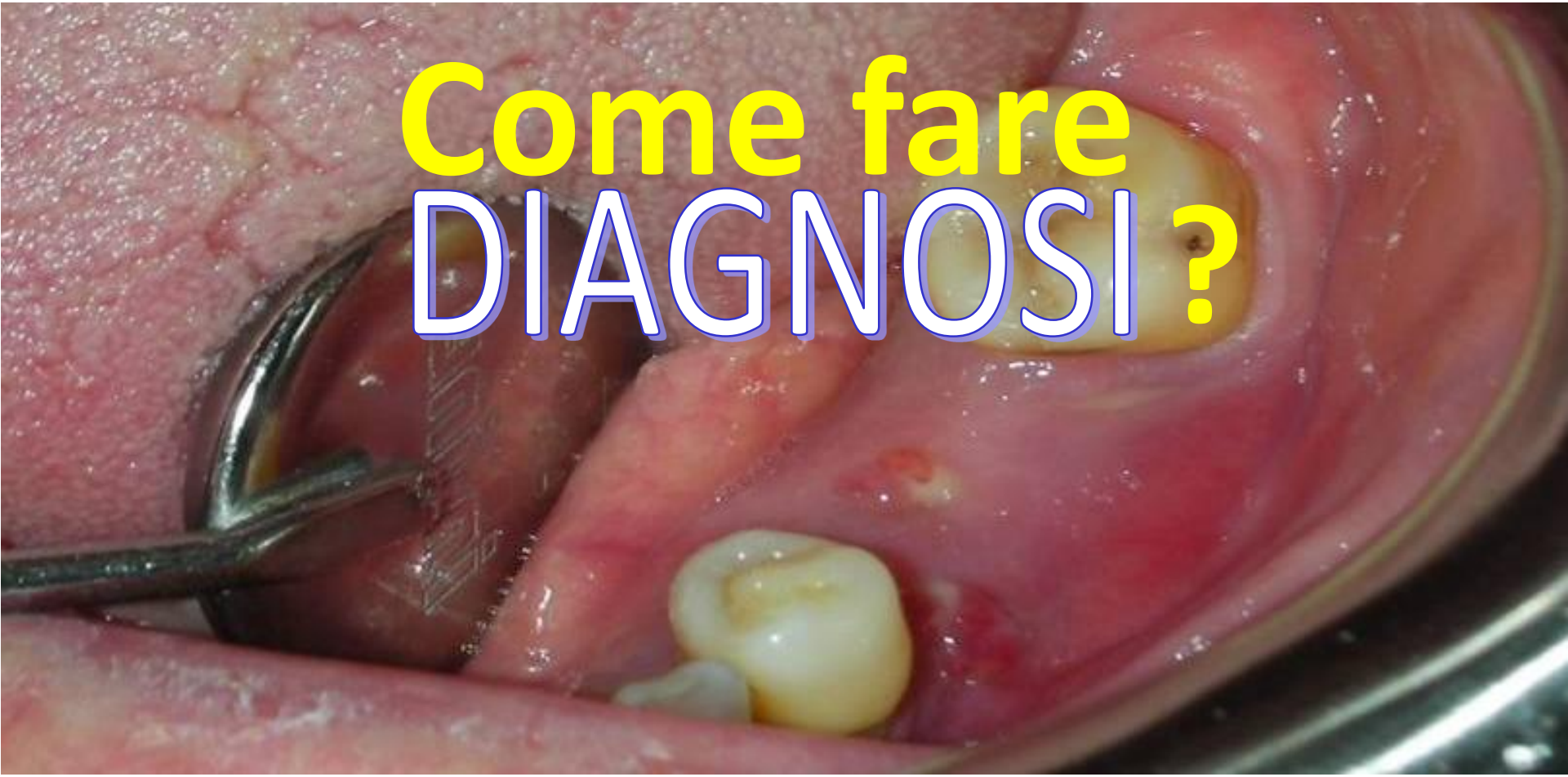
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	**Non exposed bone variant** No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone,(i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor

any stage according SS-SS

STAGE 1a according SS-SS

STAGE 1b according SS-SS

STAGE 2a, 2b and 3 according SS-SS



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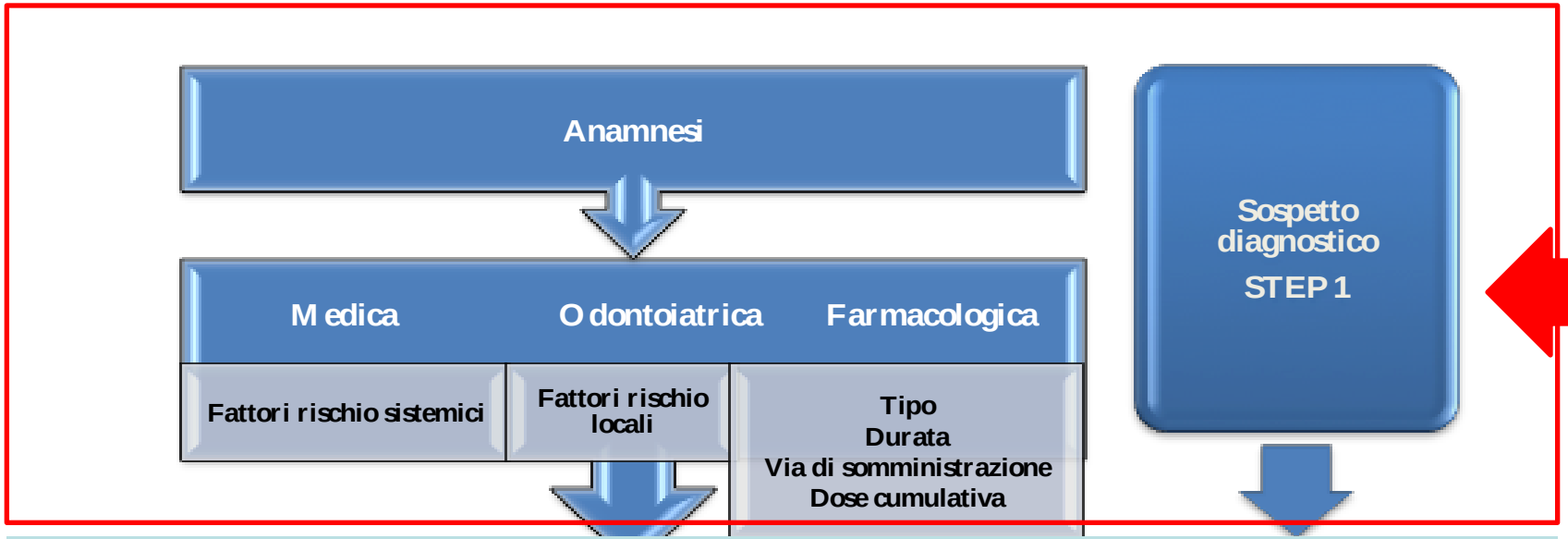
Anamnesi
Medica
Odontoiatrica
Farmacologica
Fattori rischio sistemici
Fattori rischio locali
Tipo
Durata
Via di somministrazione
Dose cumulativa
Sospetto diagnostico
STEP 1

Fattori di rischio – *Farmaco-correlati e* ***Sistemici***

Farmaco -molecola (zoledronato e denosumab *vs* altri) - via di somministrazione (endovena *vs* orale) - dose cumulativa - durata del trattamento	
Patologia di base (per cui indicata terapia): - tumori solidi - mieloma multiplo - patologia non oncologica (dismetabolica)	
Terapie di supporto: - chemioterapia - steroidi nei pazienti oncologici - steroidi nei pazienti con malattia non oncologica (dismetabolici) - antiangiogenetici nei pazienti oncologici - talidomide - fattori di stimolazione eritropoietica	

Stili di vita: - fumo - alcool - obesità	
Caratteristiche anagrafiche: - sesso - età - fattori genetici	
Patologie concomitanti (comorbidità): - diabete - artrite reumatoide - ipocalcemia, iperparatiroidismo - osteomalacia, ipovitaminosi D - insufficienza renale in dialisi - anemia	
Altre condizioni - immunodepressione - ipertensione - vasculopatie - dislipidemie - sindrome da iperviscostà	

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Ann Rheum Dis. 2014 Apr 30. doi: 10.1136/annrheumdis-2013-205080. [Epub ahead of print]

Gender related difference in the risk of bisphosphonate associated atypical femoral fracture and osteonecrosis of the jaw.

Kharazmi M[1], Hallberg P, Michaëlsson K.

Based on the results of this analysis, we conclude that the relative abundance of reports of AF among women compared with men is not entirely related to greater use of bisphosphonates but also to gender per se. We therefore propose that female gender should be considered as a risk factor for AF. Our results showed no statistically significant gender difference in the risk for ONJ, which further strengthens the theory of different mechanisms for the two ADRs. A limitation of our study is, however, the low number of men included in the analysis affecting the precision of the risk estimates.

Fattori di rischio- *Locali*

Chirurgia dento-alveolare - Estrazione dentale - Chirurgia ossea - Chirurgia endodontica - Chirurgia parodontale - Chirurgia preimplantare	
Implantologia osteointegrata	
Patologia infiammatoria dento-parodontale o peri-implantare - Parodontopatia cronica - Infezioni odontogene Ascesso parodontale Ascesso endodontico - Lesione endoperiodontale - Perimplantite - Scarsa igiene orale	

Bisphosphonate related osteonecrosis of the jaws: spontaneous or dental origin?

Sarina E.C. Pichardo, MD, DDS,[a] and J.P. Richard van Merkesteyn, DDS, MD, PhD[b]
Leiden University Medical Center, Leiden, The Netherlands

Objective(s). Bisphosphonates are frequently used worldwide mostly in osteoporosis and skeletal bone metastases. However, a serious side-effect is bisphosphonate related osteonecrosis of the jaws (BRONJ). The mechanism behind BRONJ remains unclear. In literature several origins are suggested. Presence of the teeth in the jaws may play an important role. Therefore in this study 45 patients were analyzed retrospectively.

Study design. Files of 45 patients with a diagnosis of BRONJ were analyzed, meaning clinical features, bisphosphonate use, dental history including luxating moment and (previous) treatment.

Results. In 97.5% ($n = 44$) a certain or presumable dental focus, such as extractions, a previous dental treatment or prosthesis complaints were found as initiating factor of BRONJ.

Conclusion. In contrast to findings in literature, in our group of patients a dental focus was found in 44 of 45 cases. This implies a dentoalveolar start of BRONJ with subsequent spreading into the jaws in nearly all cases. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:287-292)

Bisphosphonate related osteonecrosis of the jaws: spontaneous or dental origin?

Sarina E.C. Pichardo, MD, DDS,[a] and J.P. Richard van Merkesteyn, DDS, MD, PhD[b]

Table III. Overview literature origin BRONJ

Author	*Year*	*No. of patients*	*Administration route*	*Spontaneous (%)*	*Dental focus (%)*
Badros[20]	2008	97	IV	53	47
Bagan[21]	2006	20	IV	55	45
Bamias[11]	2005	17	IV	11.8	88.2
Bedogni[12]	2008	11	IV	18.1	81.9
Boonyapakorn[22]	2007	22	IV	23	77
Dimopoulos[13]	2006	15	IV	13.3	86.7
Durie[26]	2005	152	IV	19-31	69-81
Estilo[23]	2008	35	IV	40	51.4
Ficarra[14]	2005	9	IV	0	100
Filleul[24]	2010	2400	B	26	74
Kos[15]	2009	34	IV	0	91.2
Lugassy[25]	2004	3	IV	66.7	33.3
Maerevoet[26]	2005	9	IV	1	0
Manfredi[9]	2011	25	B	28	72
Marx[7]	2005	119	B	25.2	74.8
Marx[27]	2007	30	OR	50	50
Mavrokokki[16]	2007	112	B	21	79
Melo[17]	2005	11	IV	9.1	91.85
Merigo[8]	2006	29	B	48.3	51.7
Migliorati[28]	2005	17	IV	60	40
O'Ryan[29]	2012	30	OR	33.3	66.7
Otto[19]	2011	66	B	0	100
Pichardo	2013	45	B	0	97.8
Pires[30]	2005	12	IV	33	67
Purcell and Boyd[31]	2005	13	B	62	38
Rugierro[32]	2004	63	B	14.1	86
Saad[33]	2011	89	IV	35.1	64.9
Then[34]	2012	29	B	34.5	65.5
Thumbigere-Math[35]	2012	576	IV	41	59
Vescovi[36]	2010	567	B	31.7	68.3
Vescovi[37]	2012	151	B	29.1	70.9
Wang[38]	2003	3	IV	33.3	66.7
Watters[39]	2012	109	IV	33.9	59.7
Woo[40]	2007	368	B	40	60
Zarychanski[18]	2006	12	IV	17	83

IV, intravenously; *OR*, orally; *B*, both orally and intravenously.

Oral Health Risk Factors for Bisphosphonate-Associated Jaw Osteonecrosis

Claudine Tsao, BDSC, MPH, PhD, Ivan Darby, BDS, PhD, DiplGenDentPrac,† Peter R. Ebeling, MBBS, MD,‡ Katrina Walsh, BSc, PhD,§ Neil O'Brien-Simpson, BSc, PhD,‖ Eric Reynolds, BSc, PhD,¶ and Gelsomina Borromeo, BSc, BDSc, MScMed, PhD#*

Purpose: To investigate the role of oral health, including periodontitis, as a risk factor for bisphosphonate-associated jaw osteonecrosis (ONJ).

Materials and Methods: This cross-sectional study compared cases with an ONJ history to controls. All had a history of bisphosphonate treatment for malignancy. Participants underwent oral examination, gingival crevicular fluid (GCF) sampling, and phlebotomy. Serum was analyzed for biochemical parameters, bone markers, and immunoglobulin G titers against 4 periodontitis-associated bacteria. Cytokine levels were determined in GCF using a multiplex assay.

Results: Caries development was comparable between groups. Periodontitis was significantly associated with ONJ using the US National Center for Health Statistics periodontitis definition ($P = .002$), at least 1 site with a probing depth of at least 4 mm ($P = .003$), and the percentage of sites per participant with a probing depth of 4 to 5 mm ($P = .044$). Immunoglobulin G titer against *Porphyromonas gingivalis* and GCF interleukin-1β level were also significantly associated with ONJ ($P = .018$ and $P = .044$, respectively).

Conclusion: In participants with a history of bisphosphonate treatment for malignancy, periodontitis was associated with ONJ when measured using clinical parameters, serum immunoglobulin G titers against *P gingivalis*, and GCF interleukin-1β levels, suggesting that periodontitis and associated bacteria are potentially important in ONJ pathophysiology.

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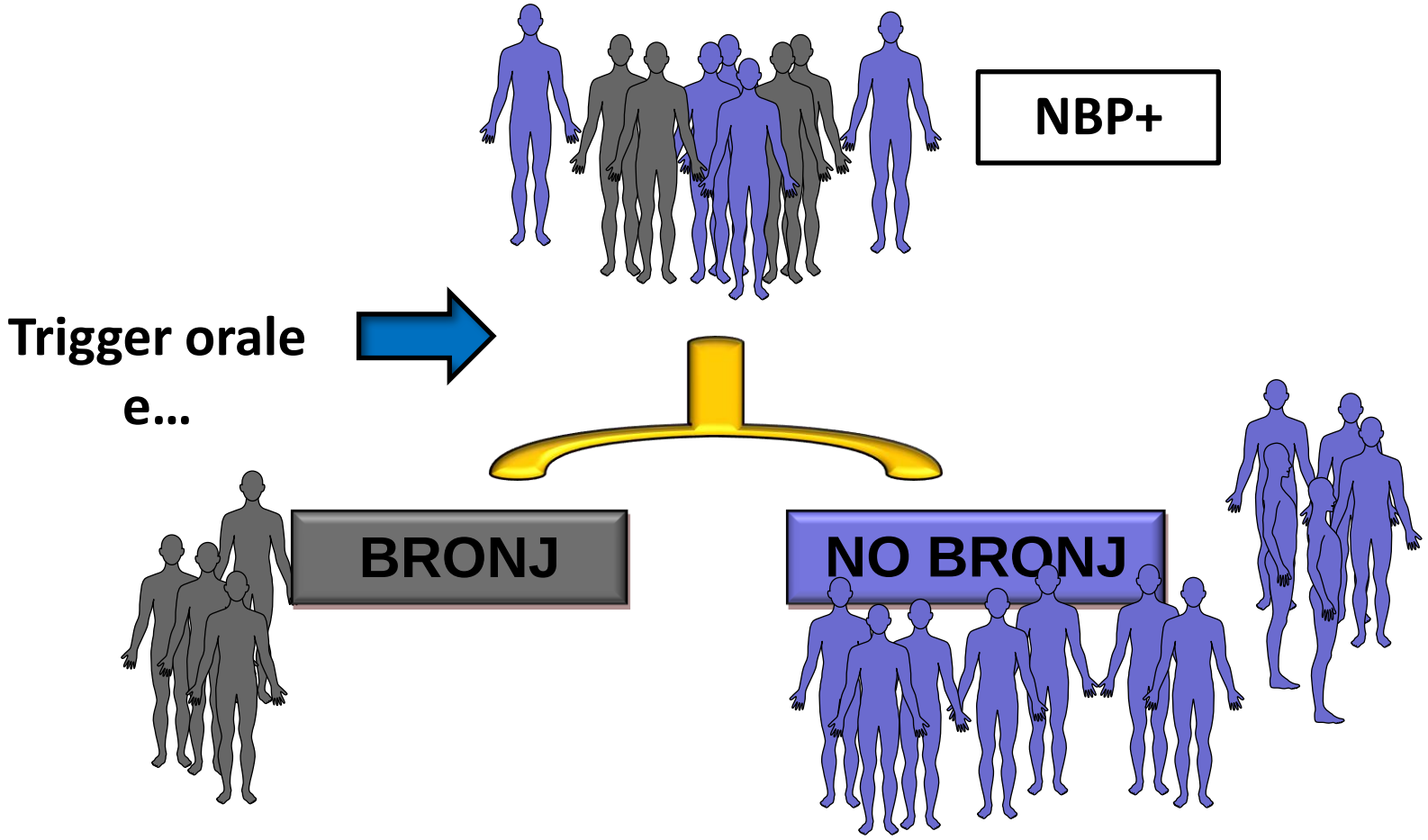
J Oral Maxillofac Surg 71:1360-1366, 2013

Fattori di rischio- *Locali*

Protesi rimovibili incongrue	
Condizioni anatomiche - Torus palatino - Tori linguali - Esostosi - Cresta miloioidea pronunciata	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J Prev Med Hyg. 2013 Sep;54(3):138-45.

Biphosphonates-associated osteonecrosis of the jaw: the role of gene-environment interaction.

Izzotti A, Menini M, Pulliero A, Dini G, Cartiglia C, Pera P, Baldi D.

Abstract

Biphosphonate (BPN) are widely used in clinics to treat metastatic cancer and osteoporosis thus representing a problem not only for patients but alsc for workers involved in their preparation and administration. A similar exposure occurred years ago in match-making workers undergoing bone alterations similar to those consequent to BPN exposure. Osteonecrosis of the jaw (ONJ) is a main adverse effect related to BPN administration, which is performed in millions of patients worldwide for osteoporosis and cancer therapy, thus representing an emerging problem in public health. In susceptible patients, BPN induce severe, progressive, and irreversible degeneration of facial bones, resulting in avascular ONJ often triggered by dental surgery. BPN induced ONJ occurs in subjects depending on lifestyle factors of both environmental and endogenous origins. Exogenous risk factors include cigarette smoke, alcohol consumption, bacterial infections, and cyclosporine therapy. Endogenous risk factors include systemic diseases such as diabetes or hypertension and adverse polymorphisms of genes involved in metabolism (CYPs, MTHFR), thrombosis (Factor V, Prothrombin), and detoxification (MDR). Available molecular findings provide evidence that ONJ is related to risk-factors associated with environmental mutagenesis and gene-environment interactions. This issues may be useful to identify susceptible subjects by molecular analyses in order to prevent ONJ occurrence.

J Craniomaxillofac Surg. 2013 Jan;41(1):71-5. doi: 10.1016/j.jcms.2012.10.018. Epub 2012 Dec 6.

Major histocompatibility complex class II polymorphisms are associated with the development of anti-resorptive agent-induced osteonecrosis of the jaw.

Stockmann P[1], Nkenke E, Englbrecht M, Schlittenbauer T, Wehrhan F, Rauh C, Beckmann MW, Fasching PA, Kreusch T, Mackensen A, Wullich B, Schett G, Spriewald BM.

⊕ **Author information**

Abstract

The aetiology of anti-resorptive agent-induced osteonecrosis of the jaw (ARONJ) is still under debate. Clinical and genetic risk factors are currently being investigated to help understand its pathogenesis. This case-control study analysed a large number of cancer patients (n = 230) under therapy with intravenous bisphosphonates, half of which were diagnosed with ARONJ. Multiple myeloma, greater patient age and the use of more than one bisphosphonate were identified as clinical risk factors on logistic regression analysis. In addition, 204 patients were genotyped for HLA-DRB1 and DQB1 and the allele frequencies were compared between ARONJ (n = 94) and unaffected cancer patients (n = 110). For the HLA class II alleles, a strong increase in the frequency of DRB1*15, DQB1*06:02, DRB1*01 and DQB1*05:01 was observed in the ARONJ group. These results were reinforced on analysis of the respective haplotypes, with DRB1*15-DQB1*06:02 being significantly associated with the development of ARONJ (odds ratio [OR] 2.5; 95% confidence interval [CI] 1.3-5.0). The presence of at least one of the haplotypes DRB1*15-DQB1*06:02 and DRB1*01-DQB1*05:01 was highly associated with the development of ARONJ (OR 3.0; 95% CI 1.7-5.5). The data in this study of a large number of cancer patients receiving intravenous bisphosphonates suggest that MHC class II polymorphisms represent genetic risk factors for the development of ARONJ. This result supports recent findings that inflammation and infection might play an important role in the pathogenesis of ARONJ.

ORAL DISEASES

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ORIGINAL ARTICLE

Salivary proteomics in bisphosphonate-related osteonecrosis of the jaw

V Thumbigere-Math[1], BS Michalowicz[1], EP de Jong[2], TJ Griffin[2], DL Basi[3], PJ Hughes[4], ML Tsai KK Swenson[5], L Rockwell[5], R Gopalakrishnan[6]

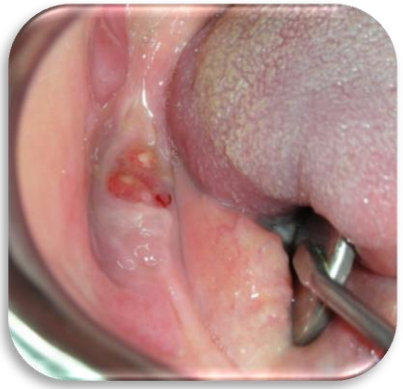
OBJECTIVE: The objective of this study was to identify differentially expressed salivary proteins in bisphosphonate-related osteonecrosis of the jaw (**BRONJ**) patients that could serve as biomarkers for **BRONJ** diagnosis.

SUBJECTS AND METHODS: Whole saliva obtained from 20 **BRONJ** patients and 20 controls were pooled within groups. The samples were analyzed using iTRAQ-labeled two-dimensional liquid chromatography–tandem mass spectrometry.

RESULTS: Overall, 1340 proteins were identified. Of these, biomarker candidates were selected based on *P*-value (<0.001), changes in protein expression (≥1.5-fold increase or decrease), and unique peptides identified (≥2). Three comparisons made between **BRONJ** and control patients identified 200 proteins to be differentially expressed in **BRONJ** patients. A majority of these proteins were predicted to have a role in drug metabolism and immunological and dermatological diseases. Of all the differentially expressed proteins, we selected metalloproteinase-9 and desmoplakin for further validation. Immunoassays confirmed increased expression of metalloproteinase-9 in individual saliva ($P = 0.048$) and serum samples ($P = 0.05$) of **BRONJ** patients. Desmoplakin was undetectable in saliva. However, desmoplakin levels tended to be lower in **BRONJ** serum than controls ($P = 0.157$).

CONCLUSIONS: Multiple pathological reactions are involved in **BRONJ** development. One or more proteins identified by this study may prove to be useful biomarkers for **BRONJ** diagnosis. The role of metalloproteinase-9 and desmoplakin in **BRONJ** requires further investigation.

DIAGNOSI

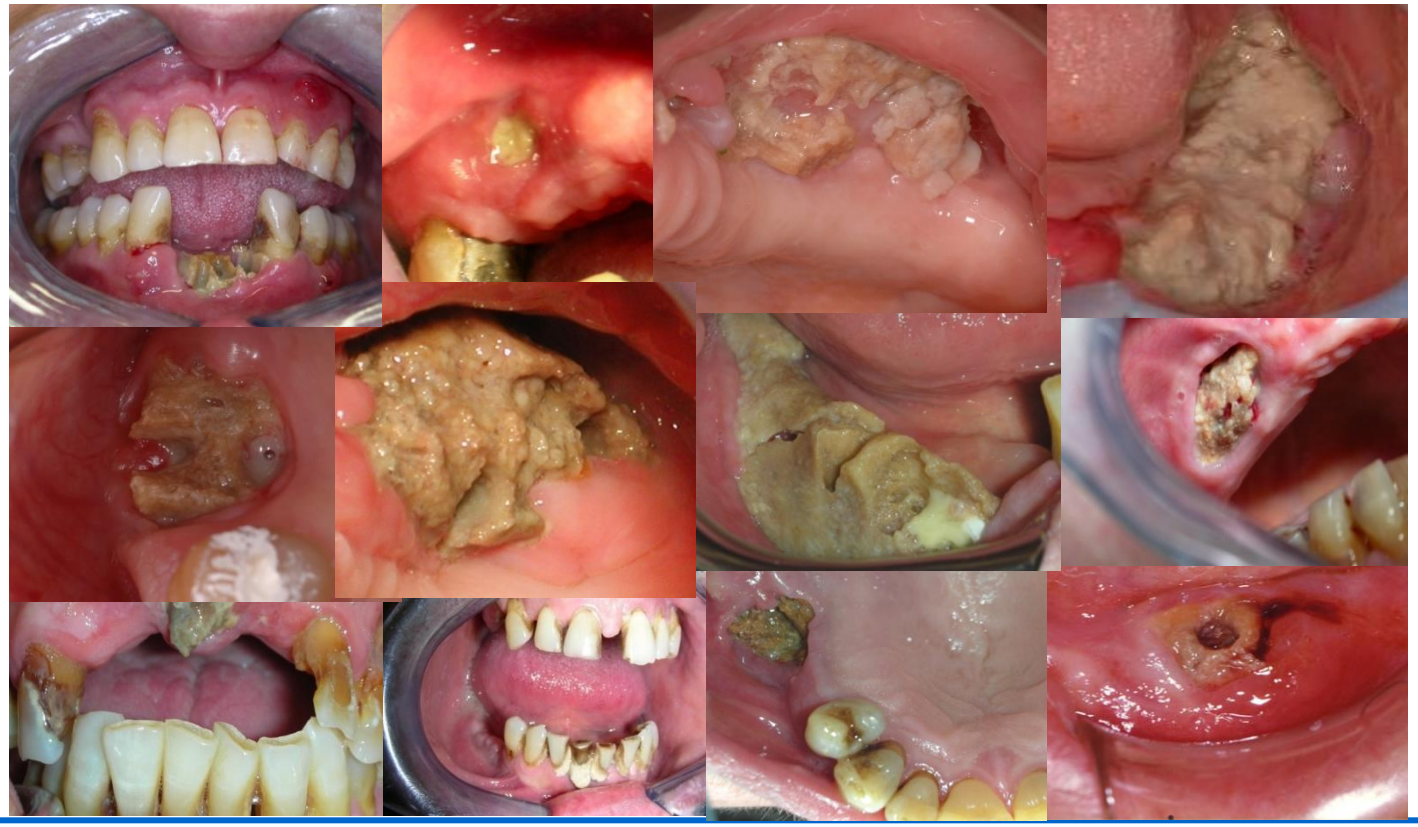


- ✓ **Segni clinici e sintomi**
- ✓ **Segni radiologici**

Segno clinico maggiore

Esposizione di osso necrotico in cavo orale

CLINICA



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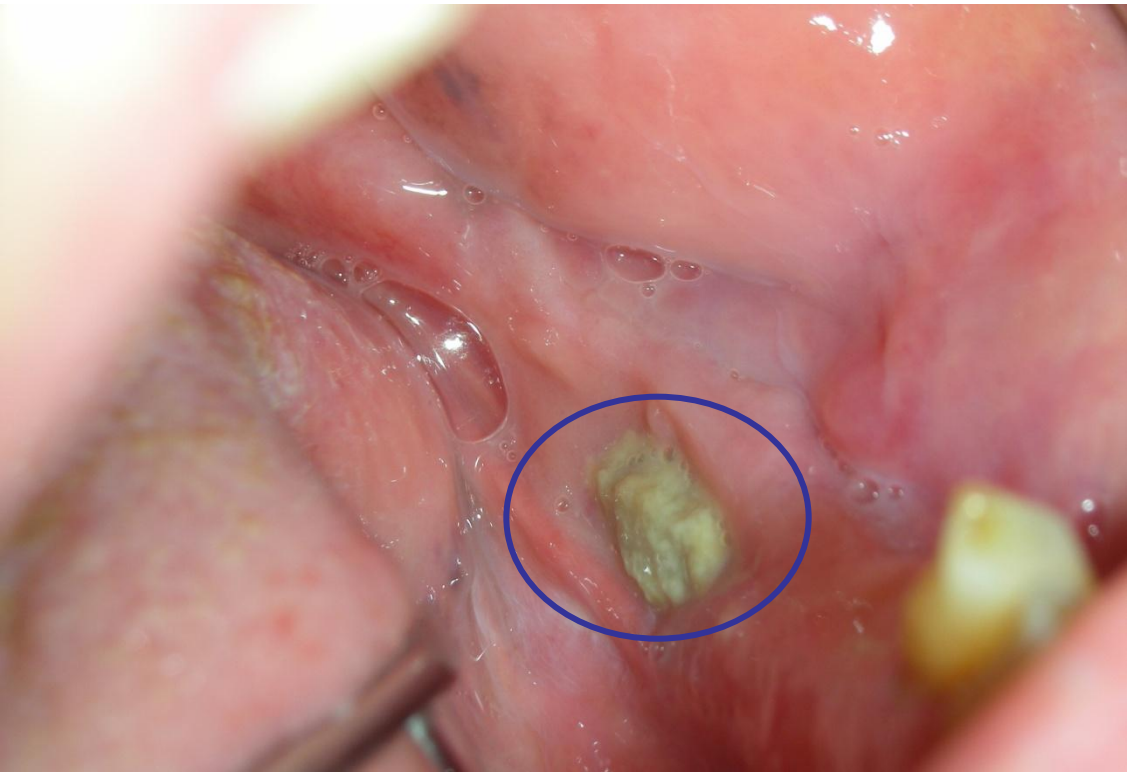

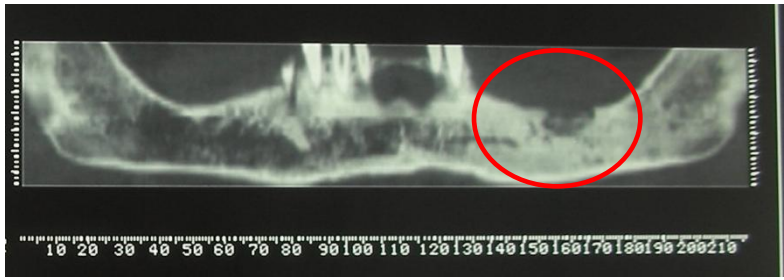
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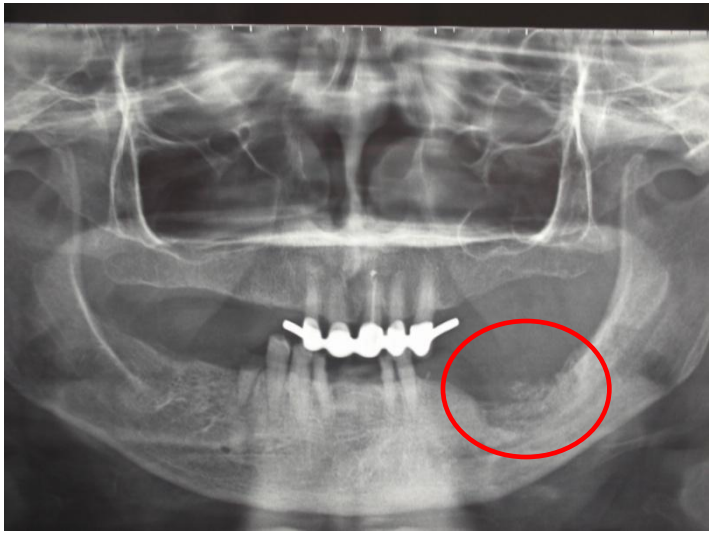
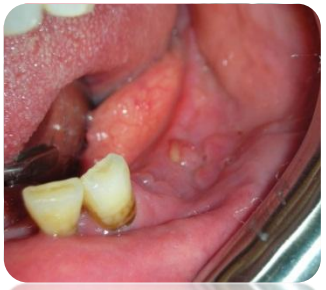


Manifestazioni cliniche BRONJ



Segno clinico maggiore

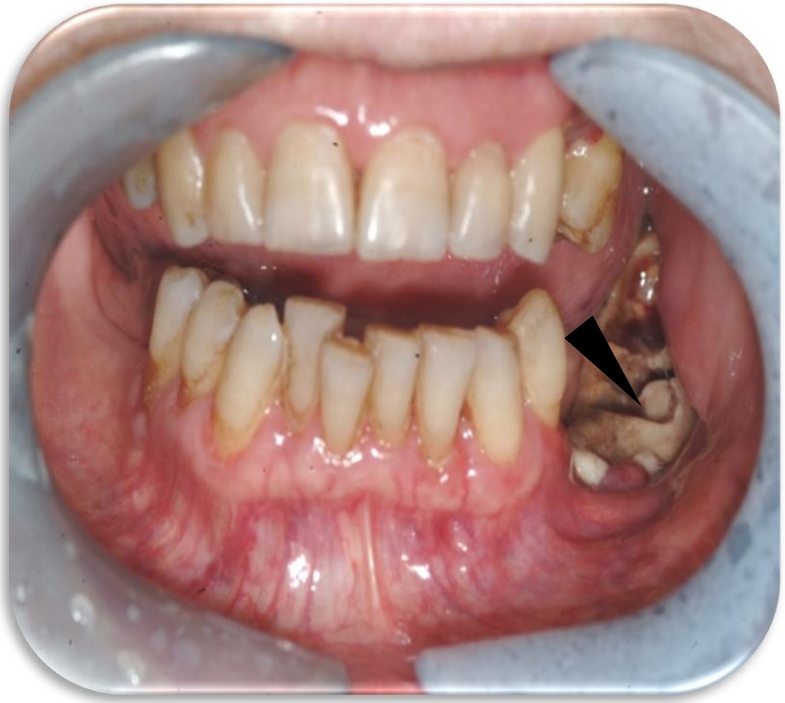
- Esposizione di osso necrotico in cavo orale

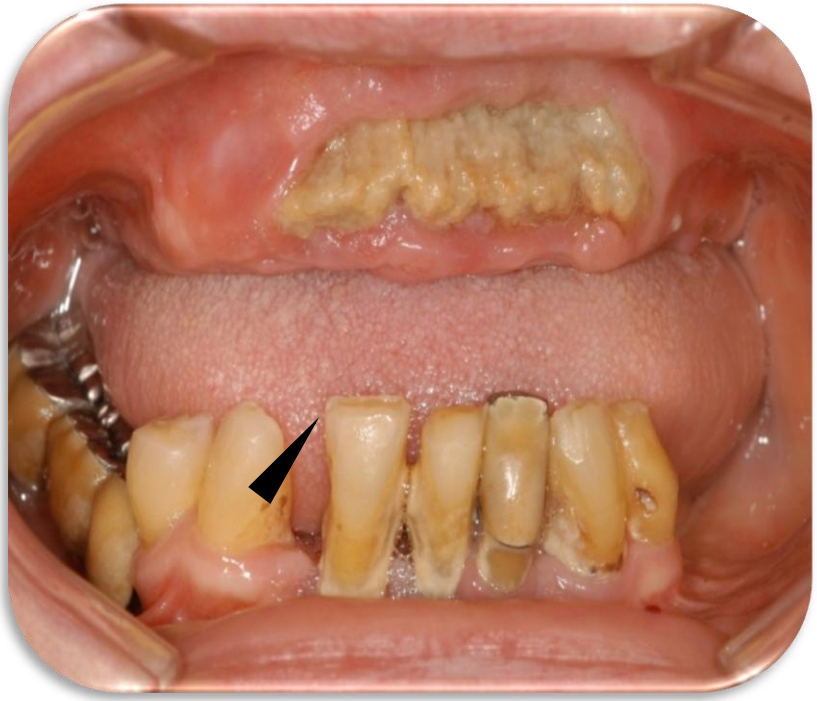
Segni clinici minori e sintomi (in ordine alfabetico)

- Ascesso odontogeno
- Asimmetria mandibolare
- Dolore di origine dentale e ossea
- Fistola mucosa
- Fistola extra-orale
- Mancata riparazione mucosa alveolare post-estrattiva
- Mobilità dentale a rapida insorgenza
- Mobilità preternaturale della mandibola, con o senza occlusione conservata
- Parestesia/disestesia delle labbra (segno di Vincent)*
- Fuoriuscita di liquidi dal naso
- Secrezione purulenta
- Sequestro spontaneo di frammenti ossei
- Trisma
- Tumefazione tessuti molli

Manifestazioni cliniche BRONJ

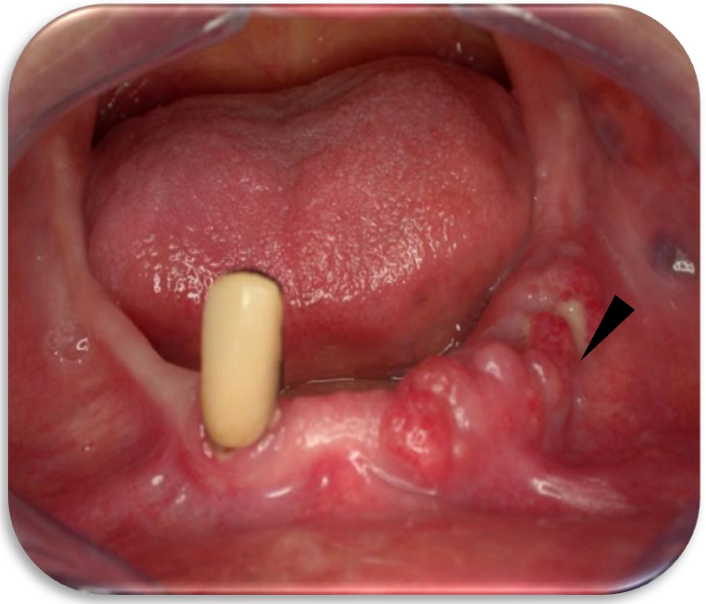
- ✓ Esposizione ossea

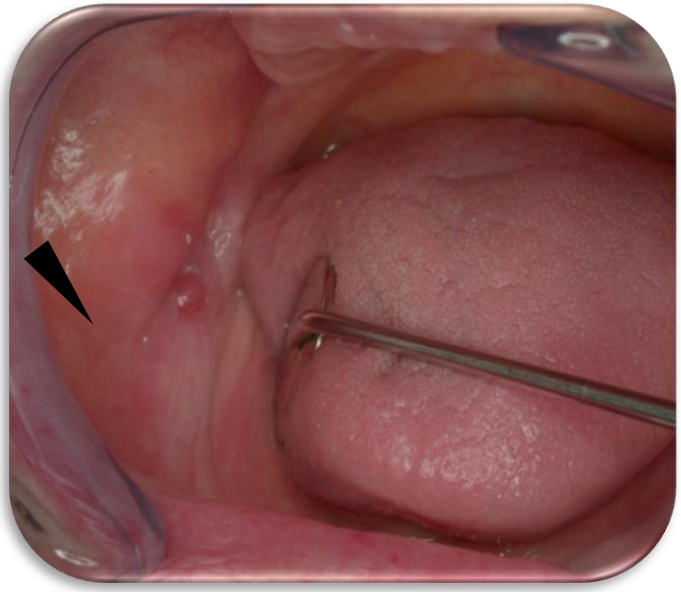




Manifestazioni cliniche BRONJ

- ✓ Alveolo post-estrattivo

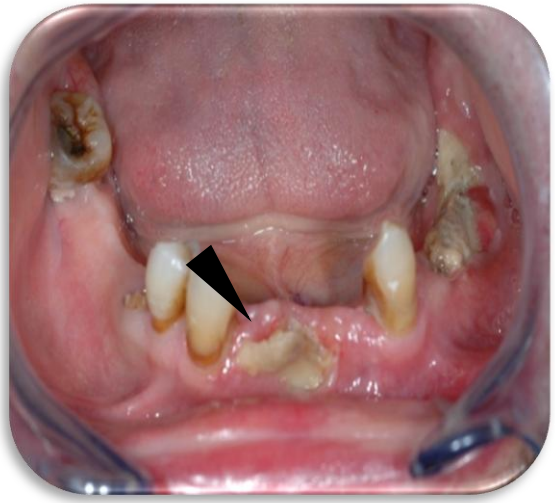


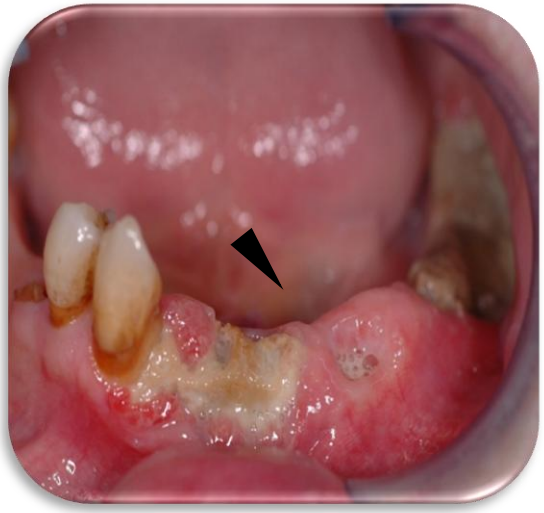


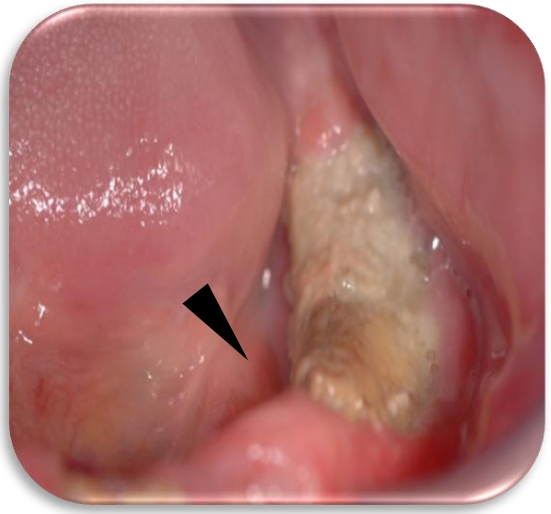
- ✓ Fistola mucosa

Manifestazioni cliniche BRONJ

- ✓ Secrezione purulenta

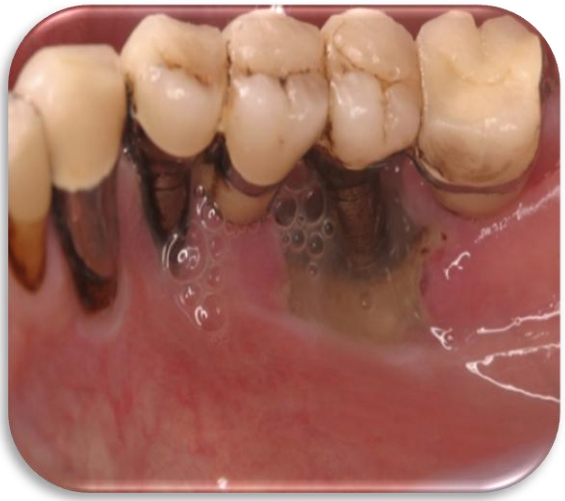
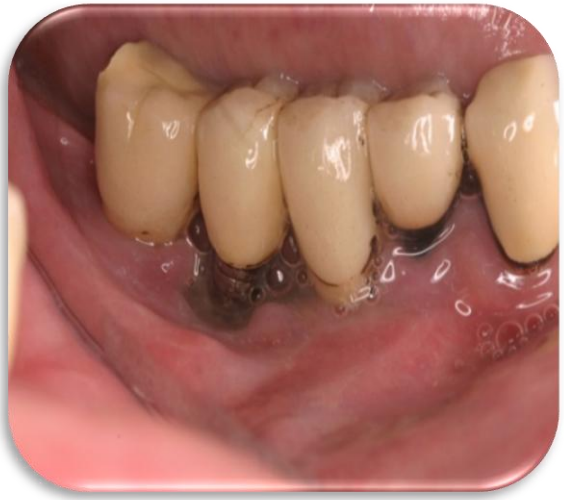
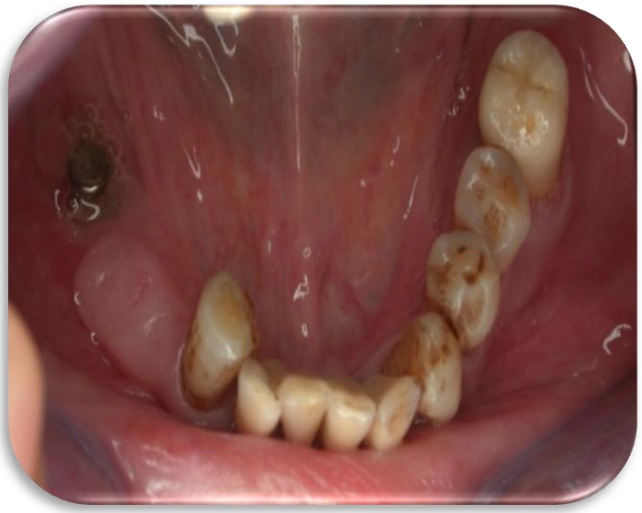






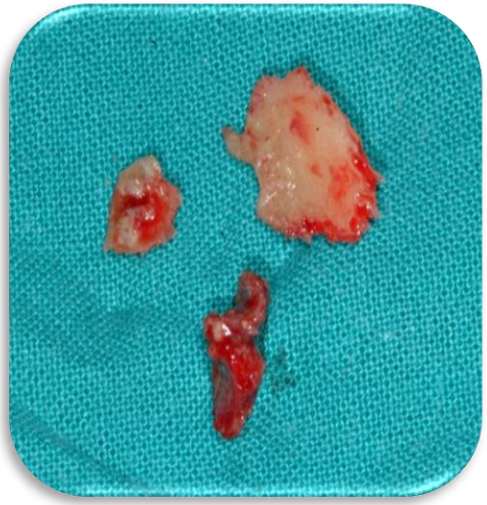
Manifestazioni cliniche BRONJ

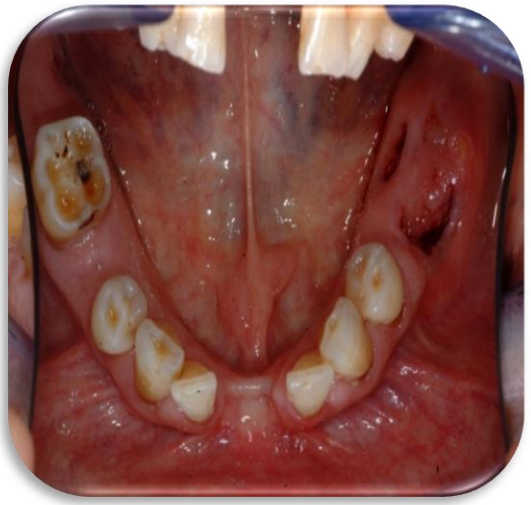
- ✓ Esposizione ossea perimplantare

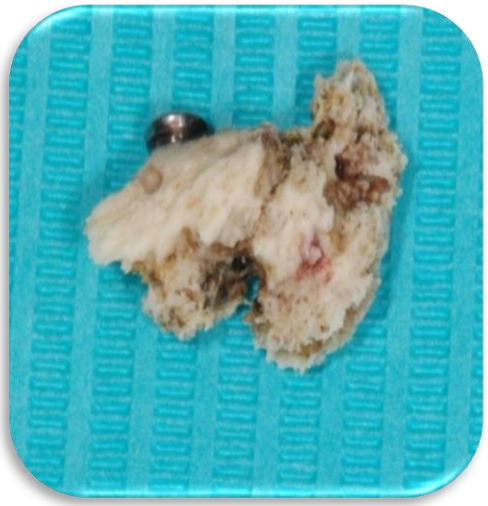




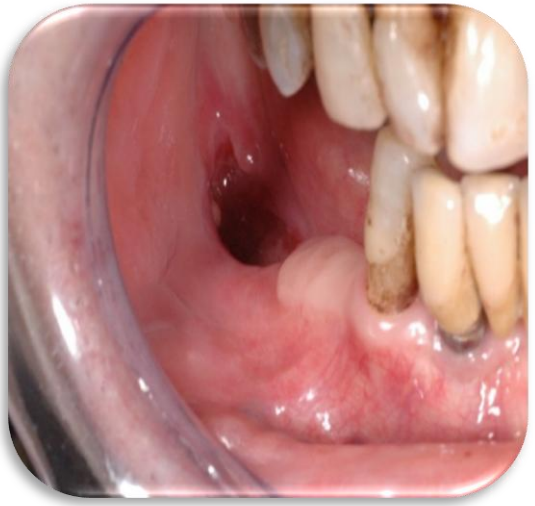
Manifestazioni cliniche BRONJ

- ✓ Autosequestrazione



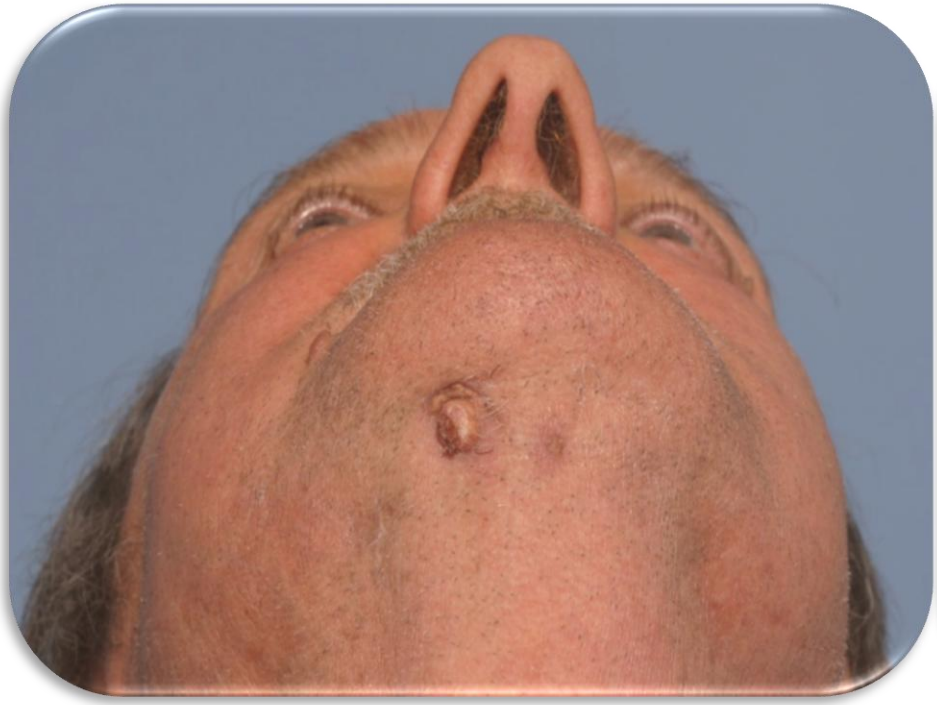


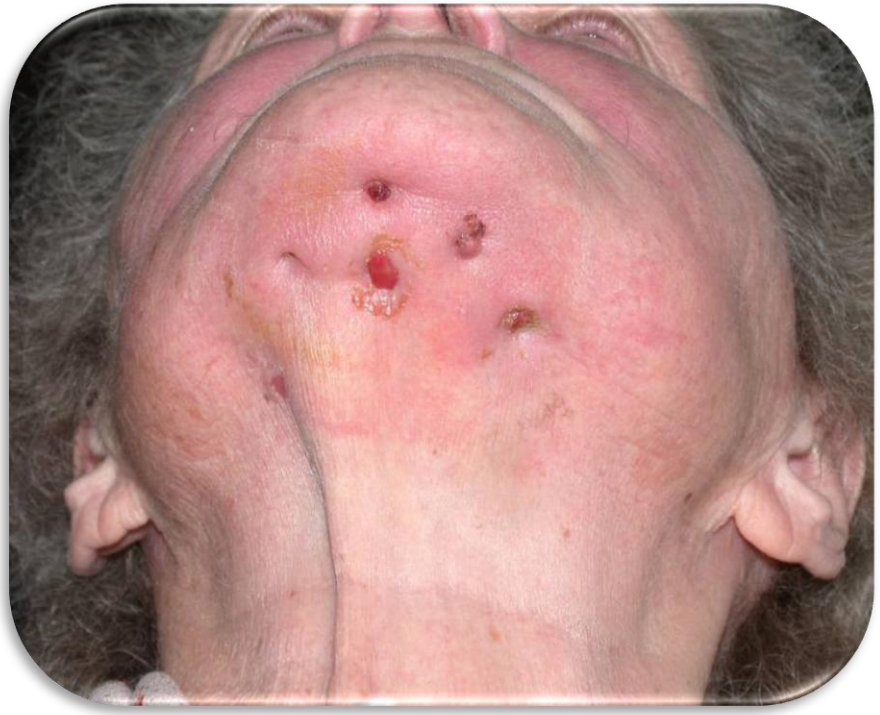




Manifestazioni cliniche BRONJ

- ✓ Fistole cutanee





Criteri diagnostici di BRONJ - Segni radiologici

*"La Commissione ritiene che l'**OPT** e la **TC** siano da considerarsi le **tecniche di indagine di primo e secondo livello rispettivamente** più utili come complemento diagnostico"*

OPT → screening iniziale (informazioni generali)

TC – spirale → discrimina con buona approssimazione tra tessuto osseo sano e patologico

Criteri diagnostici di BRONJ - Segni radiologici

	Precoci	Tardivi
OPT	- Ispessimento cresta alveolare e lamina dura - Persistenza alveolo post-estrattivo - **Sequestro** - Slargamento spazio parodontale	- Frattura patologica - Ispessimento canale NAI - **Osteosclerosi diffusa** - Radiopacità seno mascellare - Sequestro - Reazione periostale
TC	- Erosione corticale - Ispessimento cresta alveolare e lamina dura - **Ispessimento trabecolare** - **Sclerosi midollare focale** - Persistenza alveolo post-estrattivo - **Sequestro** - Slargamento spazio parodontale	- Fistola oro-antrale, oro-nasale, muco-cutanea - Frattura patologica - Ispessimento canale NAI - Osteolisi estesa al seno mascellare - **Osteosclerosi diffusa** - Reazione periostale - Sequestro - Sinusite

Stadiazione clinico-radiologica BRONJ

Stadio 1 BRONJ

BRONJ FOCALE: in presenza di almeno 1 segno clinico minore e con un *addensamento osseo alla TC limitato al solo processo dento-alveolare** della mandibola o del mascellare, con o senza altri segni radiologici precoci.

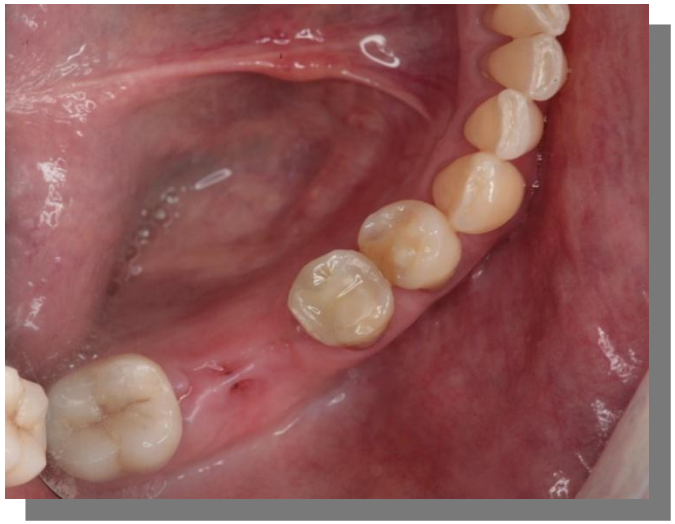
Segni clinici minori e sintomi: alitosi, ascesso odontogeno, asimmetria mandibolare, dolore di origine dentale ed osseo, esposizione ossea, fistola mucosa, mancata riparazione mucosa alveolare post-estrattiva, mobilità dentale a rapida insorgenza, parestesia/disestesia delle labbra, secrezione purulenta, sequestro spontaneo di frammenti ossei, trisma, tumefazione dei tessuti molli.

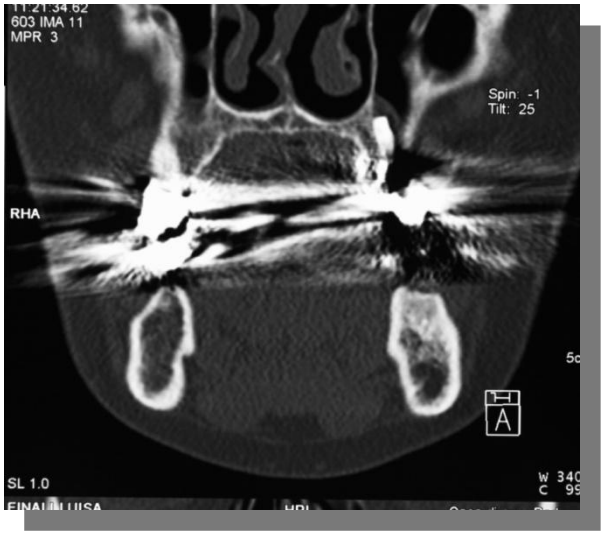
Segni TC: *ispessimento trabecolare, osteosclerosi midollare focale*, con o senza ispessimento cresta alveolare e lamina dura, persistenza alveolo post-estrattivo, slargamento spazio parodontale.

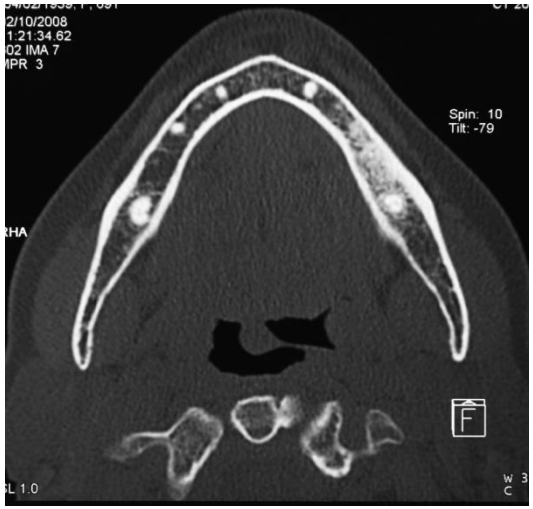
a. **asintomatica**
b. **sintomatica** (presenza di dolore e/o suppurazione)

Stadiazione clinico-radiologica BRONJ

Stadio 1 BRONJ







Pz. non oncologico

Stadiazione clinico-radiologica BRONJ

Stadio 2 BRONJ

BRONJ DIFFUSA: in presenza di almeno 1 segno clinico minore e con un *addensamento osseo alla TC esteso anche al processo basale* della mandibola o del mascellare, con o senza segni radiologici tardivi.

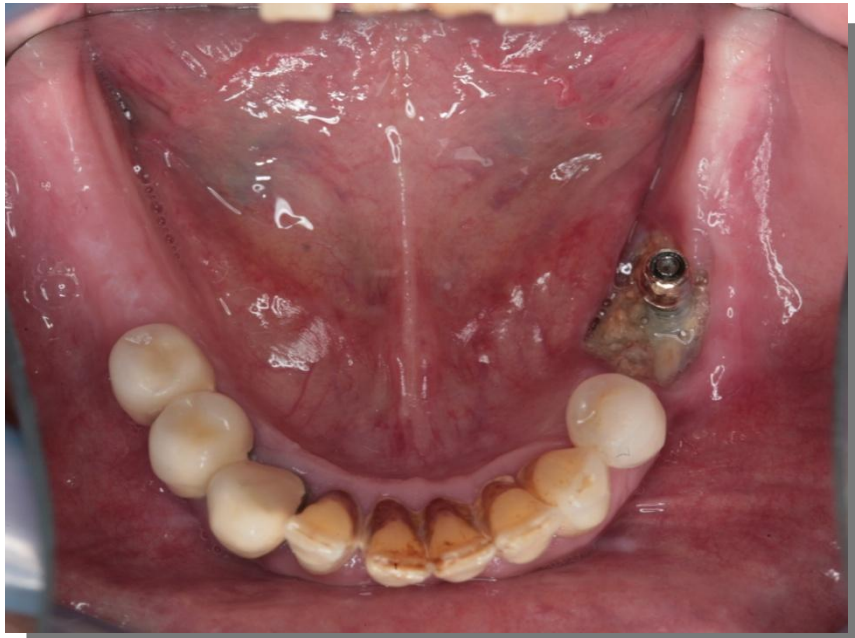
Segni clinici minori e sintomi: come per stadio 1.
Segni TC: *osteosclerosi diffusa*, con o senza fistola oro-antrale e oro-nasale, ispessimento del canale alveolare, reazione periostale, sequestro, sinusite.

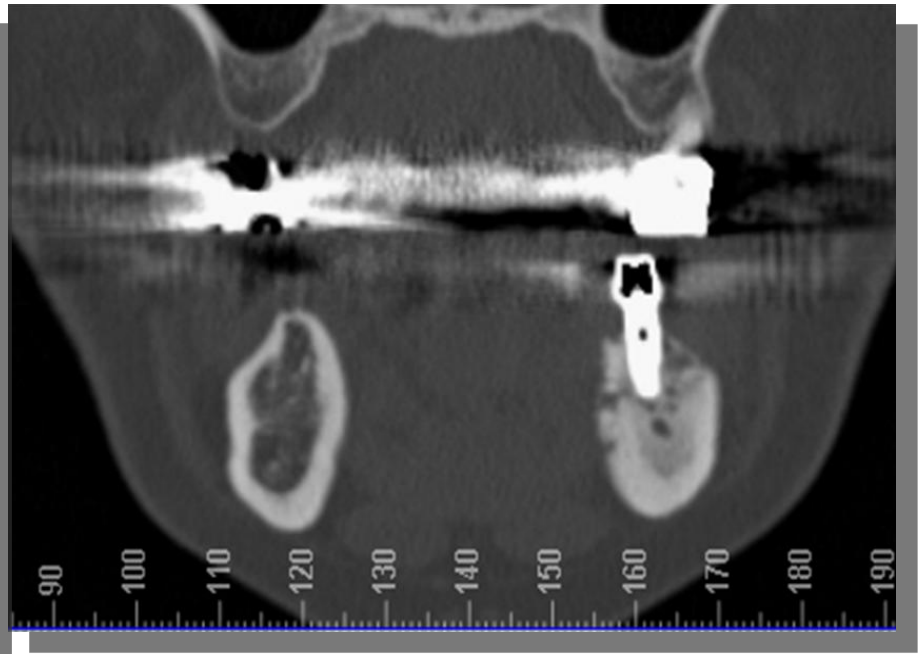
a. **asintomatica**
b. **sintomatica** (presenza di dolore e/o suppurazione)

Stadiazione clinico-radiologica BRONJ

Stadio 2 BRONJ

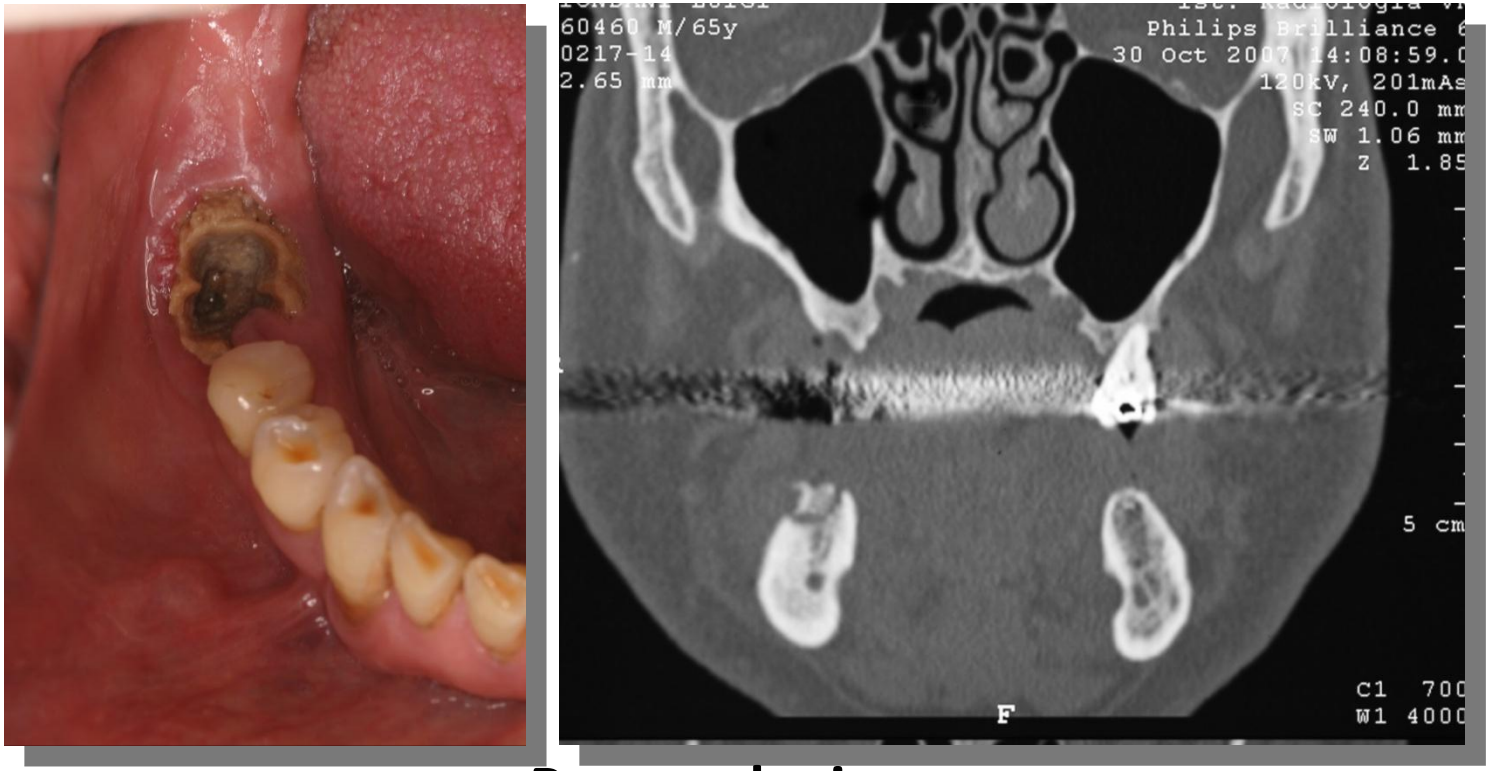
Pz. non oncologico





Stadiazione clinico-radiologica BRONJ

Stadio 2 BRONJ



Pz. oncologico

Stadiazione clinico-radiologica BRONJ

Stadio 3 BRONJ

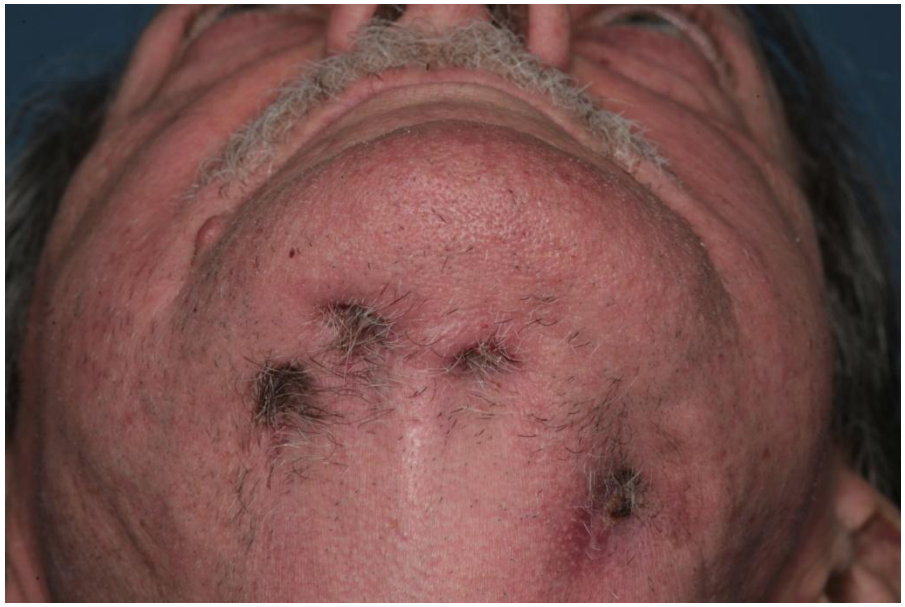
BRONJ COMPLICATA: come in stadio 2, in presenza di uno o più dei seguenti:

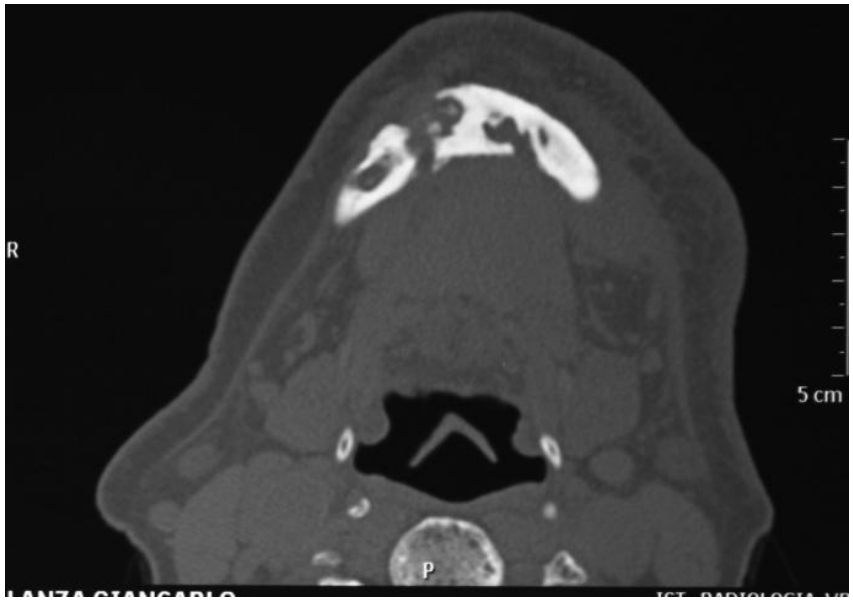
Segni clinici minori: fistola extraorale, fuoriuscita di liquidi dal naso, mobilità preternaturale della mandibola, con o senza occlusione conservata.

Segni TC: fistola muco-cutanea, Frattura patologica, osteolisi estesa al seno mascellare, osteosclerosi di zigomo e/o palato duro

Stadiazione clinico-radiologica BRONJ

Stadio 3 BRONJ





Pz. oncologico

Stadiazione clinico-radiologica BRONJ

Elementi di novità:

- ✓ **CONNOTAZIONE RADIOLOGICA** per una malattia ossea
- ✓ **DOLORE e SUPPURAZIONE** non identificano più uno stadio, bensì *distinguono forme sintomatiche e non sintomatiche all'interno di uno stesso stadio*
- ✓ **IL SEQUESTRO OSSEO** non è più considerato segno clinico peggiorativo, perchè comporta spesso un miglioramento del quadro clinico

ONJ vs METASTASIS

Vol. 117 No. 3 March 2014

Synchronous antiresorptive osteonecrosis of the jaws and breast cancer metastasis

Isadora Luana Flores, DDS, MsC, Alan Roger dos Santos-Silva, DDS, PhD, Ricardo Della Coletta, DDS, PhD, Pablo Agustin Vargas, DDS, PhD, and Márcio Ajudarte Lopes, DDS, PhD
State University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil

Antiresorptive osteonecrosis of the jaws (ARONJ) is a significant and poorly understood oral complication that may affect patients receiving antiresorptive agents, such as intravenous bisphosphonate therapy. There are scarce reports of the coexistence of ARONJ and metastasis at the same jaw site in the English-language literature. In the present case, a 60-year-old white woman was referred for the evaluation of a nonhealing extraction socket. The patient was undergoing treatment with intravenous zoledronic acid to metastatic breast cancer in bone, and her medical history and clinical characteristics led to the diagnosis of ARONJ. Nevertheless, histologic analysis showed a fragment of necrotic bone and bacterial colonies associated with malignant epithelial cells that were confirmed to be metastatic breast adenocarcinoma. This case showed that jaw metastasis can occur at the same time and site of ARONJ, making diagnosis and management challenging. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:e264-e268)

In summary, this case emphasized the necessity of microscopic/histopathologic analysis of all necrotic bone fragments resulting from debridement of clinically diagnosed ARONJ, because they can hide malignancy.

Case Report

Bisphosphonate-Related Osteonecrosis of the Jaw Mimicking Bone Metastasis

Geetika Bhatt,[1] Aashish Bhatt,[2] Anthony E. Dragun,[3] Xiao-Feng Li,[4] and A. Cahid Civelek[4]

4. Conclusion

In cancer patients receiving intravenous bisphosphonate therapy, osteonecrosis of the jaw can be easily mistaken for a metastatic site due to its clinical presentation and imaging characteristics. The practicing oncologist, the diagnostic radiologist, and/or nuclear medicine specialist and the dental specialist must all be aware of BRONJ as an entity mimicking bone metastasis. Early recognition will facilitate early diagnosis, minimize the need for biopsies and multiple unnecessary imaging studies, and, most importantly, allow appropriate treatment measures to be initiated.

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Volume 2014, Article ID 261812, 4 pages
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PRESENTAZIONE E ICONOGRAFIA A CURA DI

prof. Giuseppina Campisi

dott.sa Olga Di Fede